WO9528484

Publication Title:

HEK5, HEK7, HEK8, HEK11, NEW EPH-LIKE RECEPTOR PROTEIN TYROSINE KINASES

Abstract:

Four novel members of the EPH sub-family of receptor protein tyrosine kinases are disclosed. Nucleic acid sequences encoding receptor proteins, recombinant plasmids and host cells for expression, and methods of producing and using such receptors are also disclosed.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/12, C07K 14/71, 16/28, A61K 38/17, 39/395, C12N 15/62, G01N 33/566

A1

(11) International Publication Number: WO 95/28484

(43) International Publication Date: 26 October 1995 (26.10.95)

(21) International Application Number: PCT/US95/04681

(22) International Filing Date: 14 April 1995 (14.04.95)

(30) Priority Data:
08/229,509 15 April 1994 (15.04.94) US

(71) Applicant: AMGEN INC. [US/US]; Amgen Center, 1840 Dehavilland Drive, Thousand Oaks, CA 91320-1789 (US).

(72) Inventors: FOX, Gary, M.; 35 West Kelley Road, Newbury Park, CA 91320 (US). WELCHER, Andrew, A.; 1431 Merriman Drive, Glendale, CA 91202 (US). JING, Shuqian; 3254 Bordero Lane, Thousand Oaks, CA 91362 (US).

(74) Agents: ODRE, Steven, M. et al.; Amgen Inc., Amgen Center, 1840 Dehavilland Drive, Thousand Oaks, CA 91320-1789 (US).

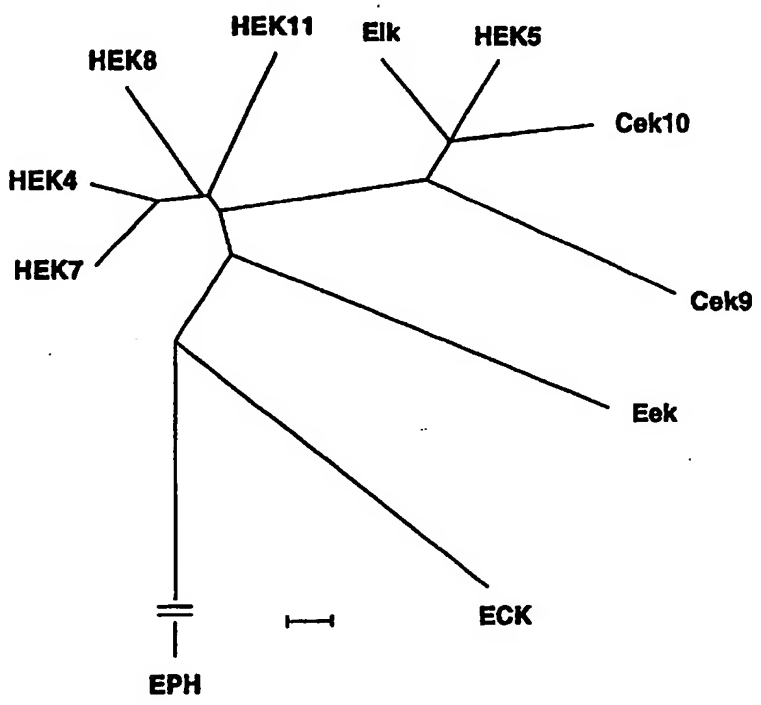
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: HEK5, HEK7, HEK8, HEK11, NEW EPH-LIKE RECEPTOR PROTEIN TYROSINE KINASES

(57) Abstract

Four novel members of the EPH subfamily of receptor protein tyrosine kinases are disclosed. Nucleic acid sequences encoding receptor proteins, recombinant plasmids and host cells for expression, and methods of producing and using such receptors are also disclosed.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

HEK5, HEK7, HEK8, HEK11, new EPH-like receptor protein tyrosine kinases

Field of the Invention

The invention relates generally to receptor protein tyrosine kinases (PTKs) and particularly to novel Eph-like receptor PTKs, to fragments and analogs thereof, and to nucleic acids encoding same. The present invention also relates to methods of producing and using such receptors.

Background of the Invention

Receptor PTKs are a structurally related family of proteins that mediate the response of cells to extracellular signals (Ullrich et al. Cell 61, 203-212 (1990)). These receptors are characterized by three major functional domains: an intracellular region containing the sequences responsible for catalytic activity, a single hydrophobic membrane-spanning domain, and a glycosylated extracellular region whose structure determines ligand binding specificity. Signal transduction is initiated by the binding of growth or differentiation factors to the extracellular domain of their cognate receptors. Ligand binding facilitates dimerization of the receptor which can induce receptor autophosphorylation. Both soluble and membrane-associated protein ligands have been shown to function in this manner. This process is the initial step in a cascade of interactions involving the phosphorylation of a variety of cytoplasmic substrates and culminating in a biological response by the cell. The best characterized response to tyrosine kinase receptor activation is cell growth. However, analysis of the role of some growth factors in vivo suggests that differentiation or cell

survival might also be mediated by tyrosine kinase receptor/ligand interactions.

Receptor PTKs have been grouped into fairly well-defined families on the basis of both sequence homology and shared structural motifs. The amino acid sequence of the portion of the intracellular domain responsible for the catalytic activity is well conserved among all tyrosine kinases and even more closely matched within a receptor sub-family. Comparisons of this portion of the amino acid sequence have been used to construct phylogenetic trees depicting the relatedness of family members to each other and to the tyrosine kinases as a whole (Hanks and Quinn, Methods Enzymol. 200, 38-62 (1991)). This sequence conservation has also been exploited in order to isolate new tyrosine kinases using the polymerase chain reaction (PCR) (Wilks, Proc. Natl. Acad. Sci. USA 86, 1603-1607 (1989)). Oligonucleotides based on the highly conserved catalytic domain of PTKs can be used as PCR primers to amplify related sequences present in the template. These fragments can then be used as probes for isolation of the corresponding full-length receptor clones from cDNA libraries. Anti-phosphotyrosine antibodies have also been used to identify PTK cDNA clones in phage expression libraries (Lindberg and Pasquale, Methods Enzymol. 200, 557-564 (1991)). These strategies have been used by a number of investigators to identify an ever-increasing number of protein tyrosine kinase receptors.

There are now 51 distinct PTK receptor genes that have been published and divided into 14 sub-families One such sub-family is the EPH-like receptors. The prototype member, EPH, was isolated by Hirai et.al. (Science 238, 1717-1720 (1987)) using low

stringency hybridization to a probe derived from the viral oncogene v-fps. EPH-like receptors have been implicated in cell growth based in part on studies which show that overexpression of the gene in NIH3T3 cells causes focus formation in soft agar and tumors in nude mice (Maru et al. Oncogene 5, 199-204 (1990)). Other members of the EPH sub-family which have been identified include the following:

ECK (Lindberg et al. Mol. Cell. Biol. 10, 6316-6324 (1990))

Elk (Lhoták et al. Mol. Cell. Biol. 11, 2496-2502 (1991))

Ceks 4,5,6,7,8,9, and 10 (Pasquale, Cell Regulation 2, 523-534 (1991); Sajjadi et al. The New Biologist 3, 769-778 (1991); Sajjadi and Pasquale Oncogene 8, 1807-1813 (1993))

HEK2 (Bohme et al. Oncogene 8, 2857-2862 (1993))

Eek, Erk (Chan and Watt, Oncogene 6, 1057-1061 (1991))

Ehk1, Ehk2 (Maisonpierre et al. Oncogene 8, 3277-3288 (1993))

Homologs for some of these receptors have been identified in other species (Wicks et al. Proc. Natl. Acad. Sci. USA 89, 1611-1615 (1992)); Gilardi-Hebenstreit et al. Oncogene 7, 2499-2506 (1992)). The expression patterns and developmental profiles of several family members suggest that these receptors and their ligands are important for the proliferation, differentiation and maintenance of a variety of tissues (Nieto et al. Development 116, 1137-1150 (1992)). Structurally, EPH sub-family members are characterized by an Ig-like loop, a cysteine rich region, and two fibronectin-type repeats in their extracellular domains. The amino acid sequences of the catalytic domains are

more closely related to the SRC sub-family of cytoplasmic PTKs than to any of the receptor PTKs. Among the catalytic domains of receptor PTKs, the EPH sub-family is most similar in amino acid sequence to the epidermal growth factor receptor sub-family.

It is an object of the invention to identify novel receptors belonging to the EPH sub-family. A directed PCR approach has been used to identify five human EPH-like receptors from a human fetal brain cDNA library. These receptors are designated HEK4, HEK5, HEK7, HEK8, and HEK11. The relationship of these receptors to previously identified EPH-like receptors is as follows:

HEK4 is the human homolog of Cek4 (chicken) and Mek4 (mouse) and is identical to HEK (Boyd et al. J. Biol. Chem. 267, 3262-3267 (1992); Wicks et al., 1992) which was previously isolated from a human lymphoid tumor cell line.

HEK5 is the human homolog of Cek5, a full-length eph-like receptor clone from chicken. A portion of the HEK5 sequence was previously disclosed as ERK, a human clone encoding about sixty amino acids (Chan and Watt, 1991)

HEK7 is the human homolog of Cek7 isolated from chicken.

HEK8 is the human homolog of Cek8 a full-length clone from chicken and Sek, a full-length clone from mouse. (Nieto et al., 1992; Sajjadi et al., 1991)

HEK11 does not have a known non-human homolog. With the addition of the new members HEK5, HEK7, HEK8 and HEK11 and the report of a PCR fragment encoding an eph-like receptor (Lai & Lemke Neuron 6, 691-704 (1991)), a total of twelve distinct sequences that represent EPH-like receptors have been published, making it the largest known sub-family of PTKs.

It is a further object of the invention to generate soluble EPH-like receptors and antibodies to EPH-like receptors. Soluble receptors and antibodies are useful for modulating EPH-like receptor activation.

Summary of the Invention

The present invention provides novel EPH-like receptor protein tyrosine kinases. More particularly, the invention provides isolated nucleic acids encoding four novel members of the sub-family of EPH-like receptor PTKs which are referred to collectively as HEKs (human-eph like kinases). Also encompassed are nucleic acids which hybridize under stringent conditions to EPH-like receptor nucleic acids. Expression vectors and host cells for the production of receptor polypeptides and methods of producing receptors are also provided.

Isolated polypeptides having amino acid sequences of EPH-like receptors are also provided, as are fragments and analogs thereof. Antibodies specifically binding the polypeptides of the invention are included. Also comprehended by the invention are methods of modulating the endogenous activity of an EPH-like receptor and methods for identifying receptor ligands.

Description of the Figures

Figure 1 shows the nucleotide and predicted amino acid sequence of the HEK5 receptor.

Figure 2 shows the nucleotide and predicted amino acid sequence of the HEK7 receptor.

Figure 3 shows the nucleotide and predicted amino acid sequence of the HEK8 receptor.

Figure 4 shows the nucleotide and predicted amino acid sequence of the HEK11 receptor.

Figure 5 shows the comparison of the amino acid sequences of the human EPH receptor sub-family. The multiple sequence alignment was done using the LineUp program included in the Genetics Computer Group sequence analysis software package (Genetics Computer Group, (1991), Program Manual for the GCG Package, Version 7, April 1991, Madison, Wisconsin, USA 53711). Dots indicate spaces introduced in order to optimize alignment. The predicted transmembrane domains and signal sequences of each receptor are indicated by underlining and italics, respectively. Cysteine residues conserved throughout the sub-family are indicated with asterisks. Arrows indicate the tyrosine kinase catalytic domain. Amino acid sequences of EPH, ECK and HEK2 were taken from the appropriate literature references.

Figure 6 shows the molecular phylogeny of the EPH sub-family of receptor protein tyrosine kinases. Catalytic domain sequences were analyzed as described by Hanks and Quinn, 1991. The scale bar represents an arbitrary evolutionary difference unit. The EPH branch, which has been shown with a discontinuity for the sake of compactness, is 23.5 units in length.

Figures 7-11 show Northern blot analyses of the tissue distribution of the HEK receptors. Receptor cDNA probes, labeled with ^{32}P, were hybridized to either 2 µg of poly A^+ RNA from human tissues (panel A, Clontech) or 10 µg of total RNA from rat tissues (panel B). Sizes of the transcripts were determined by comparison with RNA molecular weight markers (Bethesda Research Labs,

Gaithersburg, MD). Figure 7, HEK4; Figure 8, HEK5; Figure 9, HEK7; Figure 10; HEK8; Figure 11; HEK 11.

Detailed Description of the Invention

The present invention relates to novel EPH-like receptor protein tyrosine kinases. More particularly, the invention relates to isolated nucleic acids encoding four novel members of the sub-family of EPH-like receptor PTKs. These four members are designated herein as HEK (human eph-like kinases). Nucleic acids encoding HEK receptors were identified in a human fetal brain cDNA library using oligonucleotide probes to conserved regions of receptor PTKs and EPH-like receptor PTKs. The predicted amino acid sequences of three HEK receptors had extensive homology in the catalytic domain to previously identified EPH-like receptors Cek5, Cek7 and Cek8 isolated from chicken and, accordingly, are designated HEK5, HEK7 and HEK8. The predicted amino acid sequence of the fourth HEK receptor revealed that it was not a homolog of any previously identified EPH-like receptor. It is designated HEK11. It is understood that the term "HEKs" comprises HEK5, HEK7, HEK8 and HEK11 as well as analogs, variants, and mutants thereof which fall within the scope of the invention.

The invention encompasses isolated nucleic acids selected from the group consisting of:

(a) the nucleic acids set forth in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, or SEQ ID NO: 16 and their complementary strands;

(b) a nucleic acid hybridizing to the coding regions of the nucleic acids in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, or SEQ ID NO: 16 under stringent conditions; and

(c) a nucleic acid of (b) which, but for the degeneracy of the genetic code, would hybridize to the coding regions of the nucleic acids in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, or SEQ ID NO: 16. The nucleic acids of the invention preferably hybridize to HEK5, HEK7, HEK8, or HEK11 coding regions under conditions allowing up to about 5% nucleotide mismatch based upon observed nucleic acid identities among known human or nonhuman EPH-like receptors. An example of such a condition is hybridization at 60° in 1M Na^+ followed by washing at 60° in 0.2XSSC. Other hybridization conditions may be ascertained by one skilled in the art which allow base pairing with similar levels of mismatch.

In a preferred embodiment, the isolated nucleic acids encode polypeptides having the amino acid sequences of HEK5, HEK7, HEK8 or HEK11. A nucleic acid includes cDNA, genomic DNA, synthetic DNA or RNA. Nucleic acids of this invention may encode full-length receptor polypeptides having an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic domain, or may encode fragments such as extracellular domains which are produced in a soluble, secreted form. Nucleic acid constructs which produce soluble HEK receptors are described in Example 3. Polypeptides and fragments encoded by the nucleic acids have at least one of the biological activities of an EPH-like receptor protein tyrosine kinase, such as the ability to bind ligand.

The invention also encompasses nucleic acids encoding chimeric proteins wherein said proteins comprise part of the amino acid sequence of a HEK receptor linked to an amino acid sequence from a heterologous protein. One example of such a chimeric protein is an extracellular domain of a HEK receptor

fused to a heterologous receptor cytoplasmic domain. Example 5 describes the construction and expression of a chimeric receptor comprising the HEK8 extracellular domain with the trkB cytoplasmic domain and a second chimeric receptor comprising the HEK11 extracellular domain with the trkB cytoplasmic domain. HEK receptors may also be fused to other functional protein domains, such as an Ig domain which acts as an antibody recognition site.

The nucleic acids of the present invention may be linked to heterologous nucleic acids which provide expression of receptor PTKs. Such heterologous nucleic acids include biologically functional plasmids or viral vectors which provide genetic elements for transcription, translation, amplification, secretion, etc. One example of an expression vector suitable for producing EPH-like receptors of the present invention is pDSRα which is described in Example 3. It is understood that other vectors are also suitable for expression of EPH-like receptors in mammalian, yeast, insect or bacterial cells. In addition, in vivo expression of nucleic acids encoding EPH-like receptor PTKs is also encompassed. For example, tissue-specific expression of EPH-like receptors in transgenic animals may be readily effected using vectors which are functional in selected tissues.

Host cells for the expression of EPH-like receptor PTKs will preferably be established mammalian cell lines, such as Chinese Hamster Ovary (CHO) cells or NIH 3T3 cells, although other cell lines suitable for expression of mammalian genes are readily available and may also be used. Such host cells are transformed or transfected with nucleic acid constructs suitable for expression of an EPH-like receptor. Transformed or

transfected host cells may be used to produce suitable quantities of receptor for diagnostic or therapeutic uses and to effect targeted expression of EPH-like receptors in selected adult tissues, such as brain, kidney, and liver, or in embryonic or rapidly dividing tissues.

The present invention provides purified and isolated polypeptides having at least one of the biological properties of an EPH-like receptor (e.g. ligand binding, signal transduction). The isolated polypeptides will preferably have an amino acid sequence as shown in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16. Polypeptides of this invention may be full-length polypeptides having an extracellular domain, a transmembrane domain, and a cytoplasmic domain, or may be fragments thereof, e.g., those having only an extracellular domain or a portion thereof. It will be understood that the receptor polypeptides may also be analogs or naturally-occurring variants of the amino acid sequences shown in SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16. Such analogs are generated by amino acid substitutions, deletions and/or insertions using methods available in the art.

Polypeptides of the invention are preferably the product of expression of an exogenous DNA sequences, i.e., EPH-like receptors are preferably produced by recombinant means. Methods of producing EPH-like receptors comprising culturing host cells which have been transformed or transfected with vectors expressing an EPH-like receptor are also encompassed. EPH-like receptors, particularly fragments, may also be produced by chemical synthesis. The polypeptides so produced may be glycosylated or nonglycosylated depending upon the host cell employed, or may have a methionine residue at the amino terminal end. The polypeptides so produced

are identified and recovered from cell cultures employing methods which are conventional in the art.

EPH-like receptors of the present invention are used for the production of antibodies to the receptors. Antibodies to HEK receptors have been described in Example 4. Antibodies which recognize the polypeptides of the invention may be polyclonal or monoclonal and may be binding fragments or chimeric antibodies. Such antibodies are useful in the detection of EPH-like receptors in diagnostic assays in the purification of receptor, and in the modulation of EPH-like receptor activation.

As described in co-pending and co-owned U.S. Serial No. 08/145,616, the only known ligand for an EPH-like receptor is a protein which binds to and induces phosphorylation of the eck receptor. The ECK receptor ligand was previously identified as B61. (Holzman et al. Mol. Cell. Biol. 10, 5830-5838 (1990)). The availability of ECK receptor was important for the identification of a ligand since B61, although known, had not been previously implicated as an ECK receptor ligand. Therefore, EPH-like receptors having ligand binding domains are useful for the identification and purification of ligands. Polypeptides of the present invention may be used to identify and purify ligands for HEK5, HEK7, HEK8 and HEK11 receptors. Binding assays for the detection of potential ligands may be carried out in solution or by receptor immobilization on a solid support using methods such as those described in co-pending and co-owned U.S. Serial No. 08/145,616. Such assays may employ an isolated ligand binding domain of a HEK receptor. Alternatively, a HEK ligand binding domain fused to an Ig domain may be used to detect the presence of HEK ligand on cell surfaces.

Soluble EPH-like receptors may be used to modulate (i.e., increase or decrease) the activation of the cell-associated receptors, typically by competing with the receptor for unbound ligand. Modulation of EPH-like receptor activation may in turn alter the proliferation and/or differentiation of receptor-bearing cells. For example, based upon the observed tissue distribution of the receptors of this invention (see Table 5), soluble HEK7 receptor is likely to primarily affect proliferation and/or differentiation of brain cells, while soluble HEK5 receptor may affect primarily brain and pancreatic cells, although effects of HEK5 receptor on other tissues may not be excluded.

Antibodies to EPH-like receptors are useful reagents for the detection of receptors in different cell types using immunoassays conventional to the art. Antibodies are also useful therapeutic agents for modulating receptor activation. Antibodies may bind to the receptor so as to directly or indirectly block ligand binding and thereby act as an antagonist of receptor activation. Alternatively, antibodies may act as an agonist by binding to receptor so as to faciliate ligand binding and bring about receptor activation at lower ligand concentrations. In addition, antibodies of the present invention may themselves act as a ligands by inducing receptor activation. It is also contemplated that antibodies to EPH-like receptors are useful for selection of cell populations enriched for EPH-like receptor bearing cells. Such populations may be useful in cellular therapy regimens where it is necessary to treat patients which are depleted for certain cell types.

The isolated nucleic acids of the present inventions may be used in hybridization assays for the detection and quantitation of DNA and/or RNA coding for HEK5, HEK7, HEK8, HEK11 and related receptors. Such

assays are important in determining the potential of various cell types to express these receptors and in determining actual expression levels of HEK receptors. In addition, the nucleic acids are useful for detecting abnormalities in HEK receptor genes, such as translocations, rearrangements, duplications, etc.

Therapeutic regimens involving EPH-like receptors will typically involve use of the soluble form of the receptor contained in a pharmaceutical composition. Such pharmaecutical compositions may contain pharmaceutically acceptable carrier, diluents, fillers, salts, buffers, stabilizers and/or other materials well known in the art. Further examples of such constituents are described in Remington's Pharmaceutical Sciences 18th ed., A.R. Gennaro, ed. (1990). Administration of soluble EPH-like receptor compositions may be by a variety of routes depending upon the condition being treated, although typically administration will occur by intravenous or subcutaneous methods. Pharmaceutical compositions containing antibodies to EPH-like receptors will preferably include mouse-human chimeric antibodies or CDR-grafted antibodies in order to minimize the potential for an immune response by the patient to antibodies raised in mice. Other components of anti-EPH antibody compositions will be similar to those described for soluble receptor.

The amount of soluble Eph-like receptors or anti-Eph antibody in a pharmaceutical composition will depend upon the nature and severity of the condition being treated. Said amount may be determined for a given patient by one skilled in the art. It is contemplated that the pharmaceutical compositions of the present invention will contain about 0.01 µg to about

100 mg of soluble receptor or anti-Eph antibody per kg body weight.

A method for modulating the activation of an EPH-like receptor PTK is also provided by the invention. In practicing this method, a therapeutically effective amount of a soluble EPH-like receptor or an anti-EPH antibody is administered. The term "therapeutically effective amount" is that amount which effects an increase or decrease in the activation of an EPH-like receptor and will range from about 0.01 μg to about 100 mg of soluble receptor or anti-EPH antibody per kg body weight. In general, therapy will be appropriate for a patient having a condition treatable by soluble receptor or anti-EPH antibody and it is contemplated that such a condition will in part be related to the state of proliferation and/or differentiation of receptor-bearing cells. Based upon the tissue distribution of HEK receptors shown in Table 4, treatment with the pharmaceutical compositions of the invention may be particularly indicated for disorders involving brain, heart, muscle, lung, or pancreas. However, some HEK receptors are displayed on a wide variety of tissues, so it is understood that the effects of modulating receptor activation may not be limited to those tissues described herein.

The following examples are offered to more fully illustrate the invention, but are not to be construed as limiting the scope thereof. Recombinant DNA methods used in the following examples are generally as described in Sambrook et al. Molecular Cloning: A Laboratory Manual Cold Spring Harbor Laboratory Press, 2nd ed. (1989)

EXAMPLE 1

Cloning and Sequencing of *HEK* Receptor cDNA

We have isolated clones for five members of the EPH sub-family of receptor PTKs from a human fetal brain cDNA library. Oligonucleotides were designed based on conserved amino acid sequences within the kinase domain. Primer I was based on the amino acid sequence Trp-Thr-Ala-Pro-Glu-Ala-Ile (SEQ ID NO: 1), which is well-conserved among PTKs of many families. Primer II was based on the sequence Val-Cys-Lys-Val-Ser-Asp-Phe-Gly (SEQ ID NO: 2), which is invariant among EPH sub-family members but, except for the sequence Asp-Phe-Gly, is rarely found in other PTKs. Fully degenerate oligonucleotides corresponding to reverse translations of these protein sequences were synthesized and utilized as primers in a polymerase chain reaction (PCR) with disrupted phage from a human fetal brain cDNA library as the template. The products of this PCR reaction were cloned into the plasmid vector pUC19 and the nucleotide sequence of the inserts was determined. Of the 35 PCR inserts sequenced, 27 were recognizable as portions of PTK genes. Their correspondence to previously published sequences is summarized in Table 1.

TABLE 1

Receptor	PCR Products		Number of Clones
Elk	VCKVSDFGLSRYLQDDTSDPTYTSSLGGKIPVRWTAPEAI	(SEQ ID NO: 3)	2
HEK4, HEK7	VCKVSDFGLSRVLEDDPEAAYTT RGGKIPIRWTAPEAI	(SEQ ID NO: 4)	5*
HEK5	VCKVSDFGLSRFLEDDTSDPTYTSALGGKIPIRWTAPEAI	(SEQ ID NO: 5)	8
HEK8	VCKVSDFGMSRVLEDDPEAAYTT RGGKIPIRWTAPEAI	(SEQ ID NO: 6)	4
HEK11	VCKVSDFGLSRVIEDDPEAVYTTT GGKIPVRWTAPEAI	(SEQ ID NO: 7)	1
SRC	VCKVSDFGLAR LIEDNEYTARQ GAKFPIKWTAPEAI	(SEQ ID NO: 8)	6*
PDGF-β	VCKVSDFGLARDIMRDSNYISK GSTFLPLKWTAPEAI	(SEQ ID NO: 9)	1

An asterisk indicates that different nucleic acid sequences encoded the amino acid sequence shown.

Six PCR inserts predict amino acid sequences which are identical to a portion of SRC, although they comprise two distinct nucleotide sequences. One insert appears to code for the human platelet derived growth factor (PDGF)-β receptor. The remaining 18 PCR inserts consist of 6 distinct nucleotide sequences, all of which appear to be fragments of EPH sub-family members. One of the sequence predicts an amino acid sequence identical to the corresponding region of rat Elk (Lhotak et al., 1991)) and is likely to represent its human homolog. Two inserts predict amino acid sequences which match the translation of the PCR fragment tyro-4 (Lai and Lemke, 1991)) but are clearly distinct at the nucleotide level while two others correspond to tyro-1 and tyro-5. The sixth PCR insert has a previously unreported *EPH*-related sequence. Since five of the clones contained portions of potential EPH sub-family members for which full-length sequences had not been reported, each was radiolabeled and used as a probe to screen a human fetal brain cDNA library. Several clones corresponding to each of the five probes were isolated. For each of the five receptors, the nucleotide sequence of the clone containing the largest portion of the predicted coding region was determined.

A single cDNA clone containing the complete coding region was isolated only for *HEK4*. The portions of *HEK5, HEK7, HEK10 and HEK11* coding for the amino terminus of these receptors were not found in any of the clones. In order to obtain the complete coding sequence, the Rapid Amplification of cDNA Ends (RACE) technique was employed. In some cases, more than one round of RACE was necessary to obtain the missing portion of the coding region. Using this strategy, complete coding sequences were obtained for all clones except *HEK7* which lacked the complete leader sequence.

The DNA sequences of *HEK5*, *HEK7*, *HEK8* and *HEK11* are shown in Figures 1-4, respectively, and in SEQ ID NO: 10 (HEK5), SEQ ID NO: 12 (HEK7), SEQ ID NO: 14 (HEK 8) and SEQ ID NO: 16 (HEK11). The amino acid sequences are shown in SEQ ID NO: 11 (HEK5), SEQ ID NO: 13 (HEK7), SEQ ID NO: 15 (HEK8) and SEQ ID NO: 17 (HEK 11).

EXAMPLE 2

Analysis of HEK Receptor Sequences

HEK5, HEK7, HEK8 and HEK11 represent novel human EPH sub-family members, although homologs for all except HEK11 have been isolated from other species. We refer to human EPH receptor sub-family members as HEKs (human EPH-like kinases) following the nomenclature of Wicks et al., 1992). We have chosen names and numbers for these receptors to correspond with previously discovered members of the family in chicken (Ceks) and in mouse (Mek) (Sajjadi et al. 1991; Sajjadi and Pasquale, 1993; Pasquale, 1991). Extending the convention of designating the species of origin by the first letter, we refer to the rat homologs of the HEK receptors as Reks (rat EPH-like kinases).

HEK4 is the human homolog of the chicken receptor Cek4 (91% amino acid identity in the catalytic domain) and the mouse receptor Mek4 (96% amino acid identity in the catalytic domain). The amino acid sequence of HEK5 is very closely related (96% amino acid identity in the catalytic domain) to the chicken receptor Cek5 (Pasquale et al. J. Neuroscience 12, 3956-3967 (1992); Pasquale, 1991). HEK7 is probably the human homolog of the recently reported Cek7 (Sajjadi and Pasquale, 1993). HEK8 is likewise very closely related to Sek (Gilardi-Hebenstreit et al., 1992)) and Cek8 (95% amino acid identity in the catalytic domain) (Sajjadi

and Pasquale, 1993)). The human homologs for Cek6 and Cek9 have yet to be reported, while the human homolog of Cek10 has just recently been published. One of our human receptors has no close relatives in other species and apparently represents a novel member of the EPH sub-family. We have designated this receptor HEK11, assuming that human homologs for Cek 9 and 10 will be named HEK9 and HEK10, respectively. A summary of known EPH sub-family members is shown in Table 2.

TABLE 2

EPH receptor sub-family members

Human	Non-human homologs
EPH	None identified
ECK	None identified
None identified#	Eek
HEK4*	Cek4, Mek4
HEK5	Cek5, Nuk, ERK
None identified#	Cek6, Elk
HEK7	Cek7, Ehk1
HEK8	Cek8, Sek
None identified#	Cek9
HEK2	Cek10
HEK11	None identified
None identified	Ehk2

*published by Wicks et.al., 1992 as HEK

#Using the present nomenclature, the predicted human homolog of Eek is designated HEK3. For Cek6, the predicted human homolog is designated HEK6; For Cek9, the predicted human homolog is designated HEK9.

The predicted amino acid sequences of the four novel receptor clones and the previously known EPH sub-family members ECK (SEQ ID NO: 18), EPH (SEQ ID NO: 19), HEK2 (SEQ ID NO: 20) and HEK4 (SEQ ID NO: 21) were aligned as shown in Fig. 5. The four clones are closely related to each other and to the known EPH sub-family members. The extracellular domain sequences of all four novel receptors contain the Ig-loop, fibronectin-type III repeats, and cysteine-rich region characteristic of EPH sub-family members. The positions of the 20 cysteine residues are conserved among all sub-family members. Also completely conserved is the portion of the catalytic domain used as the basis for the EPH sub-family specific primer (Val-Cys-Lys-Val-Ser-Asp-Phe-Gly, SEQ ID NO: 2, amino acids 757-764 in Fig. 5). Table 3 summarizes the percentage of sequence identity between pairs of human EPH sub-family members. The lower portion of the table shows percent amino acid identity in the catalytic domain while the upper half shows percent amino acid identity in the extracellular region. The amino acid sequences of the EPH-like receptors are extremely well-conserved (60-89% amino acid identity) in the catalytic region but not as highly conserved in the extracellular region (38-65% amino acid identity), as would be expected for members of the same receptor sub-family.

TABLE 3

Eph family amino acid sequence comparison

extracellular domains

	EPH	ECK	HEK4	HEK5	HEK7	HEK8	HEK2	HEK11
EPH	*	47	42	38	40	43	40	42
ECK	62	*	47	41	45	46	41	46
HEK4	62	76	*	53	65	61	51	59
HEK5	60	74	81	*	52	53	63	51
HEK7	61	76	89	83	*	62	48	61
HEK8	62	76	86	85	88	*	52	57
HEK2	61	74	81	89	82	83	*	48
HEK11	60	74	83	83	85	85	80	*

Catalytic domains

Numbers shown are precent identity

Pairwise comparisons of amino acid sequences can be used to construct phylogenetic trees depicting the evolutionary relatedness of a family of molecules. Figure 6 is such a tree, which summarizes the relationships among the EPH sub-family members. Only one family member is shown from each group of cross-species homologs and the human representative was used whenever possible (refer to Table 2 for a summary of cross-species homologs). The branch lengths represent the degree of divergence between members. It has been shown previously that the EPH sub-family lies on a branch evolutionarily closer to the cytoplasmic PTKs than to other receptor PTKs (Lindberg and Hunter, 1993). Interestingly, the further one moves up the tree, the more closely related the receptors become and expression becomes more localized to the brain.

EXAMPLE 3

Construction and Expression of HEK Receptor Extracellular Domains

Soluble extracellular forms of HEK receptor proteins were constructed by deletion of DNA sequences encoding transmembrane and cytoplasmic domains of the receptors and introduction of a translation stop codon at the 3' end of the extracellular domain. A construct of the HEK5 extracellular domain had a stop codon introduced after lysine at position 524 as shown in Figure 1; the HEK7 extracellular domain was constructed with a stop codon after glutamine at position 547 as shown in Figure 2; the HEK 8 extracellular domain was constructed with a stop codon after threonine at position 547 as shown in Figure 3.

HEK extracellular domain was amplified from a human fetal brain cDNA library by PCR using primers 5' and 3' to the extracellular domain coding region.

For HEK5, the primers

5' CTGCTCGCCGCCGTGGAAGAAACG (SEQ ID NO: 22) and;

5' GCGTCTAGATTATCACTTCTCCTGGATGCTTGTCTGGTA (SEQ ID NO: 23)

were used to amplify the extracellular domain and to provide a restriction site for cloning into plasmid pDSRα. In addition, the following primers were used to provide a translational start site, the elk receptor signal peptide for expression; and a restriction site for cloning into pDSRα:

5' GCGGTCGACGCCGCCGCCATGGCCCTGGATTGCCTGCTGCTGTTCCTCCTG (SEQ ID NO: 24) and;

5' CGTTTCTTCCACGGCGGCGAGCAGAGATGCCAGGAGGAACAGCAGCAGGCA ATC (SEQ ID NO: 25)

The resulting construct resulted in fusion of DNA encoding the elk signal sequence Met-Ala-Leu-Asp-Cys-Leu-Leu-Leu-Phe-Leu-Leu-Ala-Ser (SEQ ID NO: 26) to the first codon of the HEK5 receptor.

The resulting HEK5 extracellular domain was cloned into pDSRα after digestion with SalI and XbaI and transfected into CHO cells for expression.

HEK8 extracellular domain was amplified from a human fetal brain cDNA library by PCR using primers 5' and 3' to the extracellular domain coding region. For HEK8, the primers

5' GAATTCGTCGACCCGGCGAACCATGGCTGGGAT and

5' GAATTCTCTAGATTATCATGTGGAGTTAGCCCCATCTC

were used to amplify the extracellular domain and to provide restriction sites for cloning into plasmid pDSRα.

The resulting HEK8 extracellular domain was cloned into pDSRα after digestion with SalI and XbaI and transferred CHO cells for expression.

HEK7 extracellular domain was amplified from a human fetal brain cDNA library by PCR using primers 5' and 3' to the extracellular domain coding region. For HEK7, the primers

5'TTCGCCCTATTTTCGTGTCTCTTCGGGATTTGCGACGCTCTCCGGACCCTCCTG GCCAGC and

5' GAATTCTCTAGATTATCACTGGCTTTGATCGCTGGAT

were used to amplify the extracellular domain. In addition, the following primers were used to provide a translational start site, the HEK8 receptor signal peptide sequence, and restriction site for cloning into plasmid pDSRα.

5'
GAATTCGTCGACCCGGCGAACCATGGCTGGGATTTTCTATTTCGCCCTATTTTCGT
GTCT

5' GAATTCTCTAGATTATCACTGGCTTTGATCGCTGGAT

The resulting construct resulted in fusion of DNA incoding HEK8 signal sequence Met-Ala-Gly-Ile-Phe-Tyr-Phe-Ala-Leu-Phe-Ser-Cys-Leu-Phe-Gly-Ile-Cys-Asp to the first codon of the HEK7 receptor.

The resulting HEK7 extracellular domain was cloned into pDSRα after digestion with SalI and XbaI and transfected into CHO cells for expression.

EXAMPLE 4

Antibodies to HEK Receptors

Antibodies to HEK receptor proteins were generated which recognize the extracellular domain by using bacterial fusion proteins as the antigen. Antibodies were also generated which recognize the cytoplasmic domain by using synthetic peptides as the antigen.

The methodology employed has been previously described (Harlow and Lane, In Antibodies: A Laboratory Manual, 1988). For the extracellular domain antibodies, cDNAs were inserted into the pATH vector (see Table 4 for the regions of each receptor encoded by this construct). These constructs were expressed in bacteria and the resultant TrpE-fusion proteins were purified by SDS-polyacrylamide gel electrophoresis. For the

cytoplasmic domain anti-peptide antibodies, peptides were synthesized (see Table 4 for the sequences) and covalently coupled to keyhole limpet hemocyanin . The fusion proteins and coupled peptides were used as antigens in rabbits and antisera were generated and characterized as described (Harlow and Lane, 1988). Anti-peptide antibodies were affinity purified by using a SulfoLink kit (Pierce, Rockford IL).

TABLE 4

HEK Receptor Antigens

Receptor	Peptide Sequences	Amino Acids in Fusion Protein
HEK4	CLETQSKNGPVPV	22-159
HEK5	CRAQMNQIQSVEV	31-168
HEK7	CMKVQLVNGMVPL	335-545
HEK8	CMRTQMQQMHGRMVPV	27-188
HEK11	CQMLHLHGTGIQV	187-503

EXAMPLE 5

HEK/TrkB Chimeric Receptors

1. Generation of pSJA1 encoding rat trkB cytoplasmic domain.

All of the chimeric receptors are composed of the extracellular domain and the transmembrane region of one of the HEK receptors and the intracellular portion of rat trkB. To simplify each individual construction, an intermediate or parental plasmid, called RtrkB/AflII (or pSJA1), was generated. First, without altering the coded peptide sequence, an AflII site (CTTAAG) was introduced into position 2021 (cytosine at position 2021

(C2021) to guanine at position 2026 (G2026, CTCAAG) of the rat trkB cDNA (Middlemas, et al., Mol. Cell. Biol. 11, 143-153 (1991)) by PCR aided mutagenesis. Briefly, PCR primers were synthesized based on the rat trkB cDNA sequence. Primer I encompassed C2003 to G2034 of the cDNA. This primer contained two mutations, a cytosine to thymine(T) substitution at position 2023 (C2023T) and an insertion of an adenine(A) in between T2013 and G2014. These mutations created the AflII site at position C2021 and an additional XhoI site flanking the AflII site. Primer II was in the reverse direction encompassing T2141 to A2165 of the cDNA which bore an ApaI site. The PCR fragment produced with these primers and the rat trkB cDNA template was digested with XhoI and ApaI enzymes and sub cloned into the XhoI and ApaI sites of an expression vector, pcDNA3 (InVitroGen), to generate pSJA1-b. Following, pSJA1-b was linearized with ApaI and ligated with a BanII digested rat trkB cDNA fragment (G2151 to G4697) to reconstitute a larger fragment (C2021 to G4697) including the coding sequence of the whole intracellular domain of the rat trkB protein (L442 to G790) and 1571 residues (A3131 to G4697) of the 1627 nucleotide 3'-end non-coding region of the cDNA.

2. Generation of HEK8/rat trkB (pSJA5) chimera.

HEK8/rat trkB chimera was generated with a similar strategy as mentioned above. A SalI/BsaI cDNA fragment was first isolated from plasmid TK10/FL13. This fragment included the nucleotide sequence from the beginning to T1689 of the HEK8 cDNA (Figure 3). Then, a pair of oligonucleotides was synthesized based on the HEK8 cDNA sequence. The sequence of the first oligonucleotide was the same as G1690 to C1740 of the Hek8 cDNA, with an additional C residue added to its 3'-end. The second oligonucleotide was in the reverse

orientation of the HEK8 cDNA. It contained C1694 to C1740 of the HEK8 cDNA sequence and an additional five residue motif, TTAAG, at its 5'-end. These two oligonucleotides were kinased and annealed with equal molar ratio, to create a double strand DNA fragment with the sequence of G1690 to C1740 of the HEK8 cDNA and with the BsaI and the AflII cohesive ends at its 5' and 3' ends, respectively. This fragment was ligated together with the SalI/BsaI cDNA fragment into XhoI/AflII linearized pSJA1 to generate the HEK8/RtrkB (pSJA5) chimerical construct.

3. Generation of HEK11/rat trkB (pSJA6) chimera.

To generate the HEK11/rat trkB chimera, a SalI/AccI fragment covering the sequence of nucleotide C1 to T1674 of the HEK11 cDNA (Figure 4) was first isolated from plasmid TK19T3. Then, a pair of oligonucleotides was synthesized based on the HEK11 cDNA sequence. The first oligonucleotide had the same sequence as from nucleotide A1666 to T1691 of the HEK11 cDNA, which contained the AccI site. The second oligonucleotide was in the reverse orientation of the HEK11 cDNA. It encompassed G1895 to T1919 of the HEK11 cDNA sequence. An additional ten residue motif, CCCGCTTAAG, was added to the 5'-end of this oligonucleotide to introduce an AflII site, which would be used to link the external domain and the transmembrane region of the HEK11 receptor to the intracellular domain of the rat trkB cDNA cloned in pSJA1 in the same reading frame. PCR was performed with these oligonucleotides as primers and the HEK11 cDNA as template. The PCR fragment was digested with AccI and AflII enzymes and ligated with the SalI/AccI cDNA fragment and the XhoI/AflII linearized pSJA1 to generate the HEK11/rat trkB (pSJA6) chimerical construct.

EXAMPLE 6

Tissue Distribution of HEK Receptors

The distribution of mRNA expression for HEK4, HEK5, HEK7, HEK8 and HEK11 receptors in human and rat tissues was examined by Northern blot hybridization.

Rat total RNA was prepared from tissues using the method of Chomczynski and Sacchi (Anal. Biochem 162, 156-159 (1987)). The RNA was separated by formaldehyde-agarose electrophoresis and transferred to Hybond-N membranes (Amersham, Arlington Heights, IL) using 20X SSC (Maniatis et al. 1982). The membrane was dried at 80°C in vacuo for 30 minutes, then crosslinked for 3 minutes on a UV transilluminator (Fotodyne, New Berlin, WI). The membrane was prehybridized for 2 hours at 42°C in 50% formamide, 5X SSPE, 5X Denhardt's, 0.2% SDS, and 100 µg/ml denatured herring sperm DNA (Maniatis et al. 1982). Northern blots of human tissue were purchased from Clontech (Palo Alto, CA). Probes were prepared by labeling the fragment of cDNA which encoded the extracellular domain of the receptor with ^{32}P-dCTP using a hexanucleotide random priming kit (Boehringer Mannheim, Indianapolis, IN) to a specific activity of at least $1x10^9$ cpm/ug. The probe was hybridized to the membrane at a concentration of 1-5 ng/ml at 42°C for 24 to 36 hours in a buffer similar to the prehybridization buffer except that 1X Denhardt's was used. After hybridization, the membranes were washed 2 times for 5 minutes each in 2X SSC, 0.1% SDS at room temperature followed by two 15 minute washes in 0.5X SSC, 0.1% SDS at 55°C. Blots were exposed for 1-2 weeks using Kodak XAR film (Kodak, Rochester, NY) with a Dupont Lightning Plus intensifying screen. The results are shown in Figures 7-11.

Homologs for HEK4 have been previously identified from mouse, chicken, and rat. In the adult mouse, expression is detected primarily in the brain and testis (Sajjadi et al. 1991). A slightly different pattern was found in adult chicken tissues, with the main sources of expression being the brain, liver, and kidney. Lower levels of expression were detectable in the lung and heart (Marcelle & Eichmann, Oncogene 7, 2479-2487 (1992)). A fragment of the *Rek4* gene (tyro-4) has been isolated and used to look at tissue expression in the adult rat (Sajjadi et al. 1991). The brain was the only tissue that expressed *Rek4* mRNA. However, RNA from lung or testis were not examined. Previous studies on *HEK4* only looked at the expression of the mRNA in cell lines, where it was found in one pre-B cell line and two T-cell lines (Wicks et al. 1992). The significance of this with regard to in vivo expression remains to be determined. In this study we have looked at the *HEK4* expression in human tissues, and also the expression of *Rek4* in rat tissues. The *HEK4* mRNA corresponds to a single transcript with a size of about 7 kb (Fig 7A). *HEK4* mRNA was most abundantly expressed in placenta, with lower levels present in heart, brain, lung, and liver. On prolonged exposures, trace amounts of mRNA were detectable in kidney and pancreas. Expression in the rat was more similar to that detected in the mouse and chicken. *Rek4* was expressed at the lowest levels of any of the family members characterized herein. A transcript of about 7 kb was detectable in rat lung, with a lower amount detectable in brain (Fig. 7B). Also, a 4 kb transcript was expressed in rat testis. Because the transcripts were barely detectable using total RNA, some of the other rat tissues may contain amounts of *Rek4* below the level of detection.

The expression of HEK5 in adult tissues has been previously studied in chicken and rat. Studies in the chicken have identified the Cek5 protein in the brain and liver, with a smaller protein detected in the intestine. In the rat, the tyro-5 fragment detected mRNA expression only in the adult brain, though intestine was not examined (Lai and Lemke, 1991). Our results show that *HEK5* mRNA was expressed at much higher levels than *HEK4* and was found as transcripts of several sizes. The most abundant mRNAs were of approximately 4.0 and 4.4 kb, with lesser amounts of higher molecular weight transcripts of 9.5 kb and longer (Fig. 8A). The *HEK5* mRNA was most abundantly expressed in placenta, but was also highly expressed in brain, pancreas, kidney, muscle, and lung. Longer exposures of the blots revealed the presence of transcripts in heart and liver as well. The rat homolog of *HEK5* (*Rek5*) showed a somewhat similar pattern of expression. *Rek5* was most abundant in intestine, followed by brain, kidney, lung, thymus, stomach, and ovary (Fig. 8B). Expression was not detectable in testis, muscle, heart, or liver. During our analysis of this family, we concluded that the rat *Erk* fragment (Chan & Watt, 1991) likely encodes a portion of the Rek5 receptor. *Erk* expression was examined in several rat tissues and found only in the lung. The reason for the discrepancy between that report and what we and others (Lai & Lemke, 1991) have found is unclear.

Homologs for *HEK8* have been identified from chicken, mouse, and rat. In the adult chicken, a single *Cek8* transcript was found to be expressed at high levels in the brain, with expression also detected in the kidney, lung, muscle, and thymus. The expression of the mouse homolog of *HEK8*, *Sek*, has been detected as a single transcript with abundant expression in the adult

brain and lower expression in the heart, lung and kidney. A fragment of *Rek8* (tyro-1) was used to look at expression in rat tissues, with expression found only in the brain (Lai & Lemke, 1991). We found that *HEK8* mRNA was expressed at levels comparable to that of *HEK5*. Multiple transcripts were also observed, the most abundant at 7 kb and 5 kb. The highest level of mRNA expression was seen in the brain, although substantial levels were detected in other tissues including heart, lung, muscle, kidney, placenta, and pancreas. Expression in liver was much lower than in the other tissues. The only difference in expression patterns between human and mouse was expression in human muscle, also seen for *Cek8* in chicken. Among the rat tissues, *Rek8* was most highly expressed in the brain, followed by the lung, heart, and testis (Fig. 10B). In contrast to *HEK8*, expression of *Rek8* appeared to be lower in muscle and kidney, two tissues where *HEK8* was readily detectable. In addition, *Rek8* was not expressed as a 5.0 kb transcript, as it was not visible even on prolonged exposures.

During the analysis of this family, we deduced that HEK7 is the human homolog of Cek7. The only expression seen in adult chicken was an 8.5 kb transcript found in the brain (Sajjadi & Pasquale, 1993). Of the five EPH sub-family members described here, *HEK7* was the most restricted in its expression pattern. Analysis of human mRNA revealed significant expression only in the brain, with a much lower level detectable in the placenta (Fig. 9A). Prolonged exposures did not reveal expression in any other tissue examined. Two prominent transcripts were found in brain, the most highly expressed with a size of 6 kb and the other with a length of 9 kb. In the placenta, however, only the 9 kb transcript was detected. *Rek7*

mRNA was expressed in a pattern similar to *HEK7*. The highest level of expression was found in brain, with a much lower level in ovary (Fig. 9B). The transcripts were of similar size as for *HEK7*, with the 6 kb transcript detected only in brain.

HEK11 was expressed as several transcripts, with major mRNAs of length 7.5, 6.0 and 3.0 kb and minor transcripts of 4.4 and 2.4 kb (Fig. 11A). All five mRNAs were expressed at the highest levels in brain, followed by heart. Placenta, lung and kidney had significant amounts of four of the five transcripts, with lower expression seen in muscle. Pancreas had barely detectable amounts of *HEK11* mRNA, while liver had no detectable *HEK11* transcript. *Rek11* had a similar pattern of expression, with four transcripts (10, 7.5, 3.5 and 3.0 kb) detected in brain (Fig. 11B).

The relative level of mRNA expression for each of the five receptors in all tissues studied is summarized in Table 5.

TABLE 5

Tissue Distribution of HEK Receptors

Human	HEK4	HEK5	HEK7	HEK8	HEK11
Brain	++	++	++	+++	++
Heart	+	+	bd	++	+
Kidney	+	+	bd	+	+
Liver	+	+	bd	+	bd
Lung	+	+	bd	++	+
Muscle	+	+	bd	++	+
Pancreas	+	++	bd	+	bd
Placenta	+++	+++	bd	++	+

Rat	HEK4	HEK5	HEK7	HEK8	HEK11
Brain	+	++	+++	+++	++
Heart	bd	bd	bd	+	bd
Intestine	bd	+++	bd	bd	bd
Kidney	bd	++	bd	bd	bd
Liver	bd	bd	bd	bd	bd
Lung	+	+	bd	++	bd
Muscle	bd	bd	bd	bd	bd
Ovary	bd	+	+	bd	bd
Stomach	bd	+	bd	bd	bd
Testis	+	bd	bd	+	bd
Thymus	bd	+	bd	bd	bd

bd= below detection

The transcripts for *HEKs* 4,5,8, and 11 were rather widely distributed in human tissue while *HEK7* was specific for brain. Expression patterns between rat and human tissue were roughly comparable given that the rat blots were less sensitive due to the use of total RNA rather than polyA$^+$. As was found for the *Cek* mRNAs by Sajjadi and Pasquale (Sajjadi & Pasquale, 1993), often there were several different size transcripts detected for a single receptor. The size distribution of the transcripts appears to be both tissue and species specific. Previous work has shown that the smaller transcript of *Mek4* encodes a potentially secreted receptor (Sajjadi et al. 1991).

The following sections describe Materials and Methods used to carry out experiments described in Example 1.

Isolation, cloning and sequencing of HEK receptor cDNAs

Fragments containing a portion of the catalytic domain of EPH sub-family receptors were generated using a polymerase chain reaction (PCR) with disrupted phage from a human fetal brain cDNA library as a template. A 10µl aliquot of the cDNA library (Stratagene, La Jolla, CA) was treated at 70°C for 5 minutes to disrupt the phage particles, then cooled on wet ice. The disrupted phage were added to 10µl of 10X Taq polymerase buffer, 8ul of 2mM each dNTP, 100 picomoles of each primer, and 1.5 µl of Taq polymerase (Promega, Madison, WI) in a total volume of 100µl. The reaction was run for 35 cycles, each consisting of 1 minute at 96°C, 1 minute at 50°C, and 2 minutes at 72°C. A 5 minute, 72°C incubation was added at the end to ensure complete extension. The primers used were degenerate mixtures of oligonucleotides based on amino

acid sequences which are highly conserved among EPH sub-family members.

5'AGGGAATTCCAYCGNGAYYTNGCNGC' (SEQ ID NO: 27);
5'AGGGGATCCRWARSWCCANACRTC'(SEQ ID NO: 28).

The products of the PCR reaction were digested with EcoRI and BamHI and cloned into M13mp19 (Messing, Methods Enzymol. (1983)) for sequence analysis. The five clones which were identified as fragments of EPH receptor sub-family members were labeled with ^{32}P-dCTP by random priming and each was used to screen Genescreen nitrocellulose filters (NEN, Boston, MA) containing plaques from the human fetal brain cDNA library. Phage stocks prepared from positively screening plaques were plated and rescreened with the same probe in order to obtain single clones. cDNA inserts were transferred into pBluescript using the in vivo excision protocol supplied with the cDNA library (Stratagene, La Jolla, CA). Nucleotide sequences were determined using Taq DyeDeoxy Terminator Cycle Sequencing kits and an Applied Biosystems 373A automated DNA sequencer (Applied Biosystems, Foster City, CA).

5' Race

The 5' ends of the cDNAs were isolated using a 5' RACE kit (GIBCO/BRL, Gaithersburg, MD) following the manufacturer's instructions. Excess primers were removed after first strand cDNA synthesis using ultrafree-MC cellulose filters (30,000 molecular weight cutoff, Millipore, Bedford, MA). Amplified PCR products were digested with the appropriate restriction enzymes, separated by agarose gel electrophoresis, and purified using a Geneclean kit (Bio101, La Jolla, CA). The purified PCR product was ligated into the plasmid vector pUC19 (Yanisch-Perron et al. Gene 33, 103-119 (1985))

which had been digested with appropriate restriction enzymes and the ligation mixture was introduced into host bacteria by electroporation. Plasmid DNA was prepared from the resulting colonies. Those clones with the largest inserts were selected for DNA sequencing.

While the present invention has been described in terms of preferred embodiments, it is understood that variations and modifications will occur to those skilled in the art. Therefore, it is intended that the appended claims cover all such equivalent variations which come within the scope of the invention as claimed.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Amgen Inc.

(ii) TITLE OF INVENTION: EPH-Like Receptor Protein Tyrosine Kinases

(iii) NUMBER OF SEQUENCES: 28

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Amgen Patent Operations/RBW
(B) STREET: 1840 Dehavilland Drive
(C) CITY: Thousand Oaks
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 91320

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Winter, Robert B.
(C) REFERENCE/DOCKET NUMBER: A-287

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Trp Thr Ala Pro Glu Ala Ile
1 5

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Val Cys Lys Val Ser Asp Phe Gly
1 5

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Tyr Leu Gln Asp Asp
1 5 10 15

Thr Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly Gly Lys Ile Pro Val
20 25 30

Arg Trp Thr Ala Pro Glu Ala Ile
35 40

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp
1 5 10 15

Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp
20 25 30

Thr Ala Pro Glu Ala Ile
35

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Phe Leu Glu Asp Asp
1 5 10 15

Thr Ser Asp Pro Thr Tyr Thr Ser Ala Leu Gly Gly Lys Ile Pro Ile
20 25 30

Arg Trp Thr Ala Pro Glu Ala Ile
35 40

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Val Cys Lys Val Ser Asp Phe Gly Met Ser Arg Val Leu Glu Asp Asp
1 5 10 15

Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp
20 25 30

Thr Ala Pro Glu Ala Ile
35

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Ile Glu Asp Asp
1 5 10 15

Pro Glu Ala Val Tyr Thr Thr Thr Gly Gly Lys Ile Pro Val Arg Trp
20 25 30

Thr Ala Pro Glu Ala Ile
35

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Val Cys Lys Val Ser Asp Phe Gly Leu Ala Arg Leu Ile Glu Asp Asn
1 5 10 15

Glu Tyr Thr Ala Arg Gln Gly Ala Lys Phe Pro Ile Lys Trp Thr Ala
20 25 30

Pro Glu Ala Ile
35

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 37 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
Val Cys Lys Val Ser Asp Phe Gly Leu Ala Arg Asp Ile Met Arg Asp
1               5                  10                  15

Ser Asn Tyr Ile Ser Lys Gly Ser Thr Phe Leu Pro Leu Lys Trp Thr
            20                  25                  30

Ala Pro Glu Ala Ile
        35
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2962 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..2913

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
CTG CTC GCC GCC GTG GAA GAA ACG CTA ATG GAC TCC ACT ACA GCG ACT      48
Leu Leu Ala Ala Val Glu Glu Thr Leu Met Asp Ser Thr Thr Ala Thr
  1               5                  10                  15

GCT GAG CTG GGC TGG ATG GTG CAT CCT CCA TCA GGG TGG GAA GAG GTG      96
Ala Glu Leu Gly Trp Met Val His Pro Pro Ser Gly Trp Glu Glu Val
            20                  25                  30

AGT GGC TAC GAT GAG AAC ATG AAC ACG ATC CGC ACG TAC CAG GTG TGC     144
Ser Gly Tyr Asp Glu Asn Met Asn Thr Ile Arg Thr Tyr Gln Val Cys
        35                  40                  45

AAC GTG TTT GAG TCA AGC CAG AAC AAC TGG CTA CGG ACC AAG TTT ATC     192
Asn Val Phe Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr Lys Phe Ile
    50                  55                  60

CGG CGC CGT GGG GCC CAC CGC ATC CAC GTG GAG ATG AAG TTT TCG GTG     240
Arg Arg Arg Gly Ala His Arg Ile His Val Glu Met Lys Phe Ser Val
65                  70                  75                  80

CGT GAC TGC AGC AGC ATC CCC AGC GTG CCT GGC TCC TGC AAG GAG ACC     288
Arg Asp Cys Ser Ser Ile Pro Ser Val Pro Gly Ser Cys Lys Glu Thr
                85                  90                  95

TTC AAC CTC TAT TAC TAT GAG GCT GAC TTT GAC TCG GCC ACC AAG ACC     336
Phe Asn Leu Tyr Tyr Tyr Glu Ala Asp Phe Asp Ser Ala Thr Lys Thr
            100                 105                 110
```

```
TTC CCC AAC TGG ATG GAG AAT CCA TGG GTG AAG GTG GAT ACC ATT GCA        384
Phe Pro Asn Trp Met Glu Asn Pro Trp Val Lys Val Asp Thr Ile Ala
        115                 120                 125

GCC GAC GAG AGC TTC TCC CAG GTG GAC CTG GGT GGC CGC GTC ATG AAA        432
Ala Asp Glu Ser Phe Ser Gln Val Asp Leu Gly Gly Arg Val Met Lys
    130                 135                 140

ATC AAC ACC GAG GTG CGG AGC TTC GGA CCT GTG TCC CGC AGC GGC TTC        480
Ile Asn Thr Glu Val Arg Ser Phe Gly Pro Val Ser Arg Ser Gly Phe
145                 150                 155                 160

TAC CTG GCC TTC CAG GAC TAT GGC GGC TGC ATG TCC CTC ATC GCC GTG        528
Tyr Leu Ala Phe Gln Asp Tyr Gly Gly Cys Met Ser Leu Ile Ala Val
                165                 170                 175

CGT GTC TTC TAC CGC AAG TGC CCC CGC ATC ATC CAG AAT GGC GCC ATC        576
Arg Val Phe Tyr Arg Lys Cys Pro Arg Ile Ile Gln Asn Gly Ala Ile
            180                 185                 190

TTC CAG GAA ACC CTG TCG GGG GCT GAG AGC ACA TCG CTG GTG GCT GCC        624
Phe Gln Glu Thr Leu Ser Gly Ala Glu Ser Thr Ser Leu Val Ala Ala
        195                 200                 205

CGG GGC AGC TGC ATC GCC AAT GCG GAA GAG GTG GAT GTA CCC ATC AAG        672
Arg Gly Ser Cys Ile Ala Asn Ala Glu Glu Val Asp Val Pro Ile Lys
    210                 215                 220

CTC TAC TGT AAC GGG GAC GGC GAG TGG CTG GTG CCC ATC GGG CGC TGC        720
Leu Tyr Cys Asn Gly Asp Gly Glu Trp Leu Val Pro Ile Gly Arg Cys
225                 230                 235                 240

ATG TGC AAA GCA GGC TTC GAG GCC GTT GAG AAT GGC ACC GTC TGC CGA        768
Met Cys Lys Ala Gly Phe Glu Ala Val Glu Asn Gly Thr Val Cys Arg
                245                 250                 255

GGT TGT CCA TCT GGG ACT TTC AAG GCC AAC CAA GGG GAT GAG GCC TGT        816
Gly Cys Pro Ser Gly Thr Phe Lys Ala Asn Gln Gly Asp Glu Ala Cys
            260                 265                 270

ACC CAC TGT CCC ATC AAC AGC CGG ACC ACT TCT GAA GGG GCC ACC AAC        864
Thr His Cys Pro Ile Asn Ser Arg Thr Thr Ser Glu Gly Ala Thr Asn
        275                 280                 285

TGT GTC TGC CGC AAT GGC TAC TAC AGA GCA GAC CTG GAC CCC CTG GAC        912
Cys Val Cys Arg Asn Gly Tyr Tyr Arg Ala Asp Leu Asp Pro Leu Asp
    290                 295                 300

ATG CCC TGC ACA ACC ATC CCC TCC GCG CCC CAG GCT GTG ATT TCC AGT        960
Met Pro Cys Thr Thr Ile Pro Ser Ala Pro Gln Ala Val Ile Ser Ser
305                 310                 315                 320

GTC AAT GAG ACC TCC CTC ATG CTG GAG TGG ACC CCT CCC CGC GAC TCC       1008
Val Asn Glu Thr Ser Leu Met Leu Glu Trp Thr Pro Pro Arg Asp Ser
                325                 330                 335
```

```
GGA GGC CGA GAG GAC CTC GTC TAC AAC ATC ATC TGC AAG AGC TGT GGC      1056
Gly Gly Arg Glu Asp Leu Val Tyr Asn Ile Ile Cys Lys Ser Cys Gly
            340                 345                 350

TCG GGC CGG GGT GCC TGC ACC CGC TGC GGG GAC AAT GTA CAG TAC GCA      1104
Ser Gly Arg Gly Ala Cys Thr Arg Cys Gly Asp Asn Val Gln Tyr Ala
        355                 360                 365

CCA CGC CAG CTA GGC CTG ACC GAG CCA CGC ATT TAC ATC AGT GAC CTG      1152
Pro Arg Gln Leu Gly Leu Thr Glu Pro Arg Ile Tyr Ile Ser Asp Leu
    370                 375                 380

CTG GCC CAC ACC CAG TAC ACC TTC GAG ATC CAG GCT GTG AAC GGC GTT      1200
Leu Ala His Thr Gln Tyr Thr Phe Glu Ile Gln Ala Val Asn Gly Val
385                 390                 395                 400

ACT GAC CAG AGC CCC TTC TCG CCT CAG TTC GCC TCT GTG AAC ATC ACC      1248
Thr Asp Gln Ser Pro Phe Ser Pro Gln Phe Ala Ser Val Asn Ile Thr
                405                 410                 415

ACC AAC CAG GCA GCT CCA TCG GCA GTG TCC ATC ATG CAT CAG GTG AGC      1296
Thr Asn Gln Ala Ala Pro Ser Ala Val Ser Ile Met His Gln Val Ser
            420                 425                 430

CGC ACC GTG GAC AGC ATT ACC CTG TCG TGG TCC CAG CCG GAC CAG CCC      1344
Arg Thr Val Asp Ser Ile Thr Leu Ser Trp Ser Gln Pro Asp Gln Pro
        435                 440                 445

AAT GGC GTG ATC CTG GAC TAT GAG CTG CAG TAC TAT GAG AAG GAG CTC      1392
Asn Gly Val Ile Leu Asp Tyr Glu Leu Gln Tyr Tyr Glu Lys Glu Leu
    450                 455                 460

AGT GAG TAC AAC GCC ACA GCC ATA AAA AGC CCC ACC AAC ACG GTC ACG      1440
Ser Glu Tyr Asn Ala Thr Ala Ile Lys Ser Pro Thr Asn Thr Val Thr
465                 470                 475                 480

GGC CTC AAA GCC GGC GCC ATC TAT GTC TTC CAG GTG CGG GCA CGC ACT      1488
Gly Leu Lys Ala Gly Ala Ile Tyr Val Phe Gln Val Arg Ala Arg Thr
                485                 490                 495

GTG GCA GGC TAC GGG CGC TAC AGC GGC AAG ATG TAC TTC CAG ACC ATG      1536
Val Ala Gly Tyr Gly Arg Tyr Ser Gly Lys Met Tyr Phe Gln Thr Met
            500                 505                 510

ACA GAA GCC GAG TAC CAG ACA AGC ATC CAG GAG AAG TTG CCA CTC ATC      1584
Thr Glu Ala Glu Tyr Gln Thr Ser Ile Gln Glu Lys Leu Pro Leu Ile
        515                 520                 525

ATC GGC TCC TCG GCC GCT GGC CTG GTC TTC CTC ATT GCT GTG GTT GTC      1632
Ile Gly Ser Ser Ala Ala Gly Leu Val Phe Leu Ile Ala Val Val Val
    530                 535                 540

ATC GCC ATC GTG TGT AAC AGA CGG GGG TTT GAG CGT GCT GAC TCG GAG      1680
Ile Ala Ile Val Cys Asn Arg Arg Gly Phe Glu Arg Ala Asp Ser Glu
545                 550                 555                 560
```

```
TAC ACG GAC AAG CTG CAA CAC TAC ACC AGT GGC CAC ATA ACC CCA GGC      1728
Tyr Thr Asp Lys Leu Gln His Tyr Thr Ser Gly His Ile Thr Pro Gly
                565                 570                 575

ATG AAG ATC TAC ATC GAT CCT TTC ACC TAC GAG GAC CCC AAC GAG GCA      1776
Met Lys Ile Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala
            580                 585                 590

GTG CGG GAG TTT GCC AAG GAA ATT GAC ATC TCC TGT GTC AAA ATT GAG      1824
Val Arg Glu Phe Ala Lys Glu Ile Asp Ile Ser Cys Val Lys Ile Glu
        595                 600                 605

CAG GTG ATC GGA GCA GGG GAG TTT GGC GAG GTC TGC AGT GGC CAC CTG      1872
Gln Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly His Leu
    610                 615                 620

AAG CTG CCA GGC AAG AGA GAG ATC TTT GTG GCC ATC AAG ACG CTC AAG      1920
Lys Leu Pro Gly Lys Arg Glu Ile Phe Val Ala Ile Lys Thr Leu Lys
625                 630                 635                 640

TCG GGC TAC ACG GAG AAG CAG CGC CGG GAC TTC CTG AGC GAA GCC TCC      1968
Ser Gly Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser
                645                 650                 655

ATC ATG GGC CAG TTC GAC CAT CCC AAC GTC ATC CAC CTG GAG GGT GTC      2016
Ile Met Gly Gln Phe Asp His Pro Asn Val Ile His Leu Glu Gly Val
            660                 665                 670

GTG ACC AAG AGC ACA CCT GTG ATG ATC ATC ACC GAG TTC ATG GAG AAT      2064
Val Thr Lys Ser Thr Pro Val Met Ile Ile Thr Glu Phe Met Glu Asn
        675                 680                 685

GGC TCC CTG GAC TCC TTT CTC CGG CAA AAC GAT GGG CAG TTC ACA GTC      2112
Gly Ser Leu Asp Ser Phe Leu Arg Gln Asn Asp Gly Gln Phe Thr Val
    690                 695                 700

ATC CAG CTG GTG GGC ATG CTT CGG GGC ATC GCA GCT GGC ATG AAG TAC      2160
Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Lys Tyr
705                 710                 715                 720

CTG GCA GAC ATG AAC TAT GTT CAC CGT GAC CTG GCT GCC CGC AAC ATC      2208
Leu Ala Asp Met Asn Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile
                725                 730                 735

CTC GTC AAC AGC AAC CTG GTC TGC AAG GTG TCG GAC TTT GGG CTC TCA      2256
Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser
            740                 745                 750

CGC TTT CTA GAG GAC GAT ACC TCA GAC CCC ACC TAC ACC AGT GCC CTG      2304
Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr Tyr Thr Ser Ala Leu
        755                 760                 765

GGC GGA AAG TTC CCC ATC CGC TGG ACA GCC CCG GAA GCC ATC CAG TAC      2352
Gly Gly Lys Phe Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr
    770                 775                 780
```

```
CGG AAG TTC ACC TCG GCC AGT GAT GTG TGG AGC TAC GGC ATT GTC ATG      2400
Arg Lys Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met
785                 790                 795                 800

TGG GAG GTG ATG TCC TAT GGG GAG CGG CCC TAC TGG GAC ATG ACC AAC      2448
Trp Glu Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Thr Asn
                805                 810                 815

CAG GAT GTA ATC AAT GCC ATT GAG CAG GAC TAT CGG CTG CCA CCG CCC      2496
Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro Pro Pro
            820                 825                 830

ATG GAC TGC CCG AGC GCC CTG CAC CAA CTC ATG CTG GAC TGT TGG CAG      2544
Met Asp Cys Pro Ser Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln
        835                 840                 845

AAG GAC CGC AAC CAC CGG CCC AAG TTC GGC CAA ATT GTC AAC ACG CTA      2592
Lys Asp Arg Asn His Arg Pro Lys Phe Gly Gln Ile Val Asn Thr Leu
    850                 855                 860

GAC AAG ATG ATC CGC AAT CCC AAC AGC CTC AAA GCC ATG GCG CCC CTC      2640
Asp Lys Met Ile Arg Asn Pro Asn Ser Leu Lys Ala Met Ala Pro Leu
865                 870                 875                 880

TCC TCT GGC ATC AAC CTG CCG CTG CTG GAC CGC ACG ATC CCC GAC TAC      2688
Ser Ser Gly Ile Asn Leu Pro Leu Leu Asp Arg Thr Ile Pro Asp Tyr
                885                 890                 895

ACC AGC TTT AAC ACG GTG GAC GAG TGG CTG GAG GCC ATC AAG ATG GGG      2736
Thr Ser Phe Asn Thr Val Asp Glu Trp Leu Glu Ala Ile Lys Met Gly
            900                 905                 910

CAG TAC AAG GAG AGC TTC GCC AAT GCC GGC TTC ACC TCC TTT GAC GTC      2784
Gln Tyr Lys Glu Ser Phe Ala Asn Ala Gly Phe Thr Ser Phe Asp Val
        915                 920                 925

GTG TCT CAG ATG ATG ATG GAG GAC ATT CTC CGG GTT GGG GTC ACT TTG      2832
Val Ser Gln Met Met Met Glu Asp Ile Leu Arg Val Gly Val Thr Leu
    930                 935                 940

GCT GGC CAC CAG AAA AAA ATC CTG AAC AGT ATC CAG GTG ATG CGG GCG      2880
Ala Gly His Gln Lys Lys Ile Leu Asn Ser Ile Gln Val Met Arg Ala
945                 950                 955                 960

CAG ATG AAC CAG ATT CAG TCT GTG GAG GTT TGACATTCAC CTGCCTCGGC        2930
Gln Met Asn Gln Ile Gln Ser Val Glu Val
                965                 970

TCACCTCTTC CTCCAAGCCC CGCCCCCTCT GC                                  2962
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 970 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Leu Leu Ala Ala Val Glu Glu Thr Leu Met Asp Ser Thr Thr Ala Thr
 1               5                  10                  15

Ala Glu Leu Gly Trp Met Val His Pro Pro Ser Gly Trp Glu Glu Val
            20                  25                  30

Ser Gly Tyr Asp Glu Asn Met Asn Thr Ile Arg Thr Tyr Gln Val Cys
        35                  40                  45

Asn Val Phe Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr Lys Phe Ile
    50                  55                  60

Arg Arg Arg Gly Ala His Arg Ile His Val Glu Met Lys Phe Ser Val
65                  70                  75                  80

Arg Asp Cys Ser Ser Ile Pro Ser Val Pro Gly Ser Cys Lys Glu Thr
                85                  90                  95

Phe Asn Leu Tyr Tyr Tyr Glu Ala Asp Phe Asp Ser Ala Thr Lys Thr
            100                 105                 110

Phe Pro Asn Trp Met Glu Asn Pro Trp Val Lys Val Asp Thr Ile Ala
        115                 120                 125

Ala Asp Glu Ser Phe Ser Gln Val Asp Leu Gly Gly Arg Val Met Lys
    130                 135                 140

Ile Asn Thr Glu Val Arg Ser Phe Gly Pro Val Ser Arg Ser Gly Phe
145                 150                 155                 160

Tyr Leu Ala Phe Gln Asp Tyr Gly Gly Cys Met Ser Leu Ile Ala Val
                165                 170                 175

Arg Val Phe Tyr Arg Lys Cys Pro Arg Ile Ile Gln Asn Gly Ala Ile
            180                 185                 190

Phe Gln Glu Thr Leu Ser Gly Ala Glu Ser Thr Ser Leu Val Ala Ala
        195                 200                 205

Arg Gly Ser Cys Ile Ala Asn Ala Glu Glu Val Asp Val Pro Ile Lys
    210                 215                 220

Leu Tyr Cys Asn Gly Asp Gly Glu Trp Leu Val Pro Ile Gly Arg Cys
225                 230                 235                 240

Met Cys Lys Ala Gly Phe Glu Ala Val Glu Asn Gly Thr Val Cys Arg
                245                 250                 255

Gly Cys Pro Ser Gly Thr Phe Lys Ala Asn Gln Gly Asp Glu Ala Cys
            260                 265                 270

Thr His Cys Pro Ile Asn Ser Arg Thr Thr Ser Glu Gly Ala Thr Asn
        275                 280                 285
```

```
Cys Val Cys Arg Asn Gly Tyr Tyr Arg Ala Asp Leu Asp Pro Leu Asp
    290                 295                 300

Met Pro Cys Thr Thr Ile Pro Ser Ala Pro Gln Ala Val Ile Ser Ser
305                 310                 315                 320

Val Asn Glu Thr Ser Leu Met Leu Glu Trp Thr Pro Pro Arg Asp Ser
                325                 330                 335

Gly Gly Arg Glu Asp Leu Val Tyr Asn Ile Ile Cys Lys Ser Cys Gly
            340                 345                 350

Ser Gly Arg Gly Ala Cys Thr Arg Cys Gly Asp Asn Val Gln Tyr Ala
        355                 360                 365

Pro Arg Gln Leu Gly Leu Thr Glu Pro Arg Ile Tyr Ile Ser Asp Leu
    370                 375                 380

Leu Ala His Thr Gln Tyr Thr Phe Glu Ile Gln Ala Val Asn Gly Val
385                 390                 395                 400

Thr Asp Gln Ser Pro Phe Ser Pro Gln Phe Ala Ser Val Asn Ile Thr
                405                 410                 415

Thr Asn Gln Ala Ala Pro Ser Ala Val Ser Ile Met His Gln Val Ser
            420                 425                 430

Arg Thr Val Asp Ser Ile Thr Leu Ser Trp Ser Gln Pro Asp Gln Pro
        435                 440                 445

Asn Gly Val Ile Leu Asp Tyr Glu Leu Gln Tyr Tyr Glu Lys Glu Leu
    450                 455                 460

Ser Glu Tyr Asn Ala Thr Ala Ile Lys Ser Pro Thr Asn Thr Val Thr
465                 470                 475                 480

Gly Leu Lys Ala Gly Ala Ile Tyr Val Phe Gln Val Arg Ala Arg Thr
                485                 490                 495

Val Ala Gly Tyr Gly Arg Tyr Ser Gly Lys Met Tyr Phe Gln Thr Met
            500                 505                 510

Thr Glu Ala Glu Tyr Gln Thr Ser Ile Gln Glu Lys Leu Pro Leu Ile
        515                 520                 525

Ile Gly Ser Ser Ala Ala Gly Leu Val Phe Leu Ile Ala Val Val Val
    530                 535                 540

Ile Ala Ile Val Cys Asn Arg Arg Gly Phe Glu Arg Ala Asp Ser Glu
545                 550                 555                 560

Tyr Thr Asp Lys Leu Gln His Tyr Thr Ser Gly His Ile Thr Pro Gly
                565                 570                 575

Met Lys Ile Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala
            580                 585                 590
```

Val Arg Glu Phe Ala Lys Glu Ile Asp Ile Ser Cys Val Lys Ile Glu
595 600 605

Gln Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly His Leu
610 615 620

Lys Leu Pro Gly Lys Arg Glu Ile Phe Val Ala Ile Lys Thr Leu Lys
625 630 635 640

Ser Gly Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser
645 650 655

Ile Met Gly Gln Phe Asp His Pro Asn Val Ile His Leu Glu Gly Val
660 665 670

Val Thr Lys Ser Thr Pro Val Met Ile Ile Thr Glu Phe Met Glu Asn
675 680 685

Gly Ser Leu Asp Ser Phe Leu Arg Gln Asn Asp Gly Gln Phe Thr Val
690 695 700

Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Lys Tyr
705 710 715 720

Leu Ala Asp Met Asn Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile
725 730 735

Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser
740 745 750

Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr Tyr Thr Ser Ala Leu
755 760 765

Gly Gly Lys Phe Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr
770 775 780

Arg Lys Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met
785 790 795 800

Trp Glu Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Thr Asn
805 810 815

Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro Pro Pro
820 825 830

Met Asp Cys Pro Ser Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln
835 840 845

Lys Asp Arg Asn His Arg Pro Lys Phe Gly Gln Ile Val Asn Thr Leu
850 855 860

Asp Lys Met Ile Arg Asn Pro Asn Ser Leu Lys Ala Met Ala Pro Leu
865 870 875 880

Ser Ser Gly Ile Asn Leu Pro Leu Leu Asp Arg Thr Ile Pro Asp Tyr
885 890 895

```
Thr Ser Phe Asn Thr Val Asp Glu Trp Leu Glu Ala Ile Lys Met Gly
            900                 905                 910

Gln Tyr Lys Glu Ser Phe Ala Asn Ala Gly Phe Thr Ser Phe Asp Val
        915                 920                 925

Val Ser Gln Met Met Met Glu Asp Ile Leu Arg Val Gly Val Thr Leu
    930                 935                 940

Ala Gly His Gln Lys Lys Ile Leu Asn Ser Ile Gln Val Met Arg Ala
945                 950                 955                 960

Gln Met Asn Gln Ile Gln Ser Val Glu Val
                965                 970
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3162 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..2976

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
CCA GCG TCC CTG GCC GGC TGC TAC TCT GCA CCT CGA CGG GCT CCC CTC        48
Pro Ala Ser Leu Ala Gly Cys Tyr Ser Ala Pro Arg Arg Ala Pro Leu
  1               5                  10                  15

TGG ACG TGC CTT CTC CTG TGC GCC GCA CTC CGG ACC CTC CTG GCC AGC        96
Trp Thr Cys Leu Leu Leu Cys Ala Ala Leu Arg Thr Leu Leu Ala Ser
            20                  25                  30

CCC AGC AAC GAA GTG AAT TTA TTG GAT TCA CGC ACT GTC ATG GGG GAC       144
Pro Ser Asn Glu Val Asn Leu Leu Asp Ser Arg Thr Val Met Gly Asp
        35                  40                  45

CTG GGA TGG ATT GCT TTT CCA AAA AAT GGG TGG GAA GAG ATT GGT GAA       192
Leu Gly Trp Ile Ala Phe Pro Lys Asn Gly Trp Glu Glu Ile Gly Glu
    50                  55                  60

GTG GAT GAA AAT TAT GCC CCT ATC CAC ACA TAC CAA GTA TGC AAA GTG       240
Val Asp Glu Asn Tyr Ala Pro Ile His Thr Tyr Gln Val Cys Lys Val
65                  70                  75                  80

ATG GAA CAG AAT CAG AAT AAC TGG CTT TTG ACC AGT TGG ATC TCC AAT       288
Met Glu Gln Asn Gln Asn Asn Trp Leu Leu Thr Ser Trp Ile Ser Asn
                85                  90                  95
```

```
GAA GGT GCT TCC AGA ATC TTC ATA GAA CTC AAA TTT ACC CTG CGG GAC      336
Glu Gly Ala Ser Arg Ile Phe Ile Glu Leu Lys Phe Thr Leu Arg Asp
            100                 105                 110

TGC AAC AGC CTT CCT GGA GGA CTG GGG ACC TGT AAG GAA ACC TTT AAT      384
Cys Asn Ser Leu Pro Gly Gly Leu Gly Thr Cys Lys Glu Thr Phe Asn
        115                 120                 125

ATG TAT TAC TTT GAG TCA GAT GAT CAG AAT GGG AGA AAC ATC AAG GAA      432
Met Tyr Tyr Phe Glu Ser Asp Asp Gln Asn Gly Arg Asn Ile Lys Glu
    130                 135                 140

AAC CAA TAC ATC AAA ATT GAT ACC ATT GCT GCC GAT GAA AGC TTT ACA      480
Asn Gln Tyr Ile Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr
145                 150                 155                 160

GAA CTT GAT CTT GGT GAC CGT GTT ATG AAA CTG AAT ACA GAG GTC AGA      528
Glu Leu Asp Leu Gly Asp Arg Val Met Lys Leu Asn Thr Glu Val Arg
                165                 170                 175

GAT GTA GGA CCT CTA AGC AAA AAG GGA TTT TAT CTT GCT TTT CAA GAT      576
Asp Val Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp
            180                 185                 190

GTT GGT GCT TGC ATT GCT CTG GTT TCT GTG CGT GTA TAC TAT AAA AAA      624
Val Gly Ala Cys Ile Ala Leu Val Ser Val Arg Val Tyr Tyr Lys Lys
        195                 200                 205

TGC CCT TCT GTG GTA CGA CAC TTG GCT GTC TTC CCT GAC ACC ATC ACT      672
Cys Pro Ser Val Val Arg His Leu Ala Val Phe Pro Asp Thr Ile Thr
    210                 215                 220

GGA GCT GAT TCT TCC CAA TTG CTC GAA GTG TCG GGC TCC TGT GTC AAC      720
Gly Ala Asp Ser Ser Gln Leu Leu Glu Val Ser Gly Ser Cys Val Asn
225                 230                 235                 240

CAT TCT GTG ACC GAT GAA CCT CCC AAA ATG CAC TGC AGC GCC GAA GGG      768
His Ser Val Thr Asp Glu Pro Pro Lys Met His Cys Ser Ala Glu Gly
                245                 250                 255

GAG TGG CTG GTG CCC ATC GGG AAA TGC ATG TGC AAG GCA GGA TAT GAA      816
Glu Trp Leu Val Pro Ile Gly Lys Cys Met Cys Lys Ala Gly Tyr Glu
            260                 265                 270

GAG AAA AAT GGC ACC TGT CAA GTG TGC AGA CCT GGG TTC TTC AAA GCC      864
Glu Lys Asn Gly Thr Cys Gln Val Cys Arg Pro Gly Phe Phe Lys Ala
        275                 280                 285

TCA CCT CAC ATC CAG AGC TGC GGC AAA TGT CCA CCT CAC AGT TAT ACC      912
Ser Pro His Ile Gln Ser Cys Gly Lys Cys Pro Pro His Ser Tyr Thr
    290                 295                 300

CAT GAG GAA GCT TCA ACC TCT TGT GTC TGT GAA AAG GAT TAT TTC AGG      960
His Glu Glu Ala Ser Thr Ser Cys Val Cys Glu Lys Asp Tyr Phe Arg
305                 310                 315                 320
```

```
AGA GAG TCT GAT CCA CCC ACA ATG GCA TGC ACA AGA CCC CCC TCT GCT      1008
Arg Glu Ser Asp Pro Pro Thr Met Ala Cys Thr Arg Pro Pro Ser Ala
                325                 330                 335

CCT CGG AAT GCC ATC TCA AAT GTT AAT GAA ACT AGT GTC TTT CTG GAA      1056
Pro Arg Asn Ala Ile Ser Asn Val Asn Glu Thr Ser Val Phe Leu Glu
            340                 345                 350

TGG ATT CCG CCT GCT GAC ACT GGT GGA AGG AAA GAC GTG TCA TAT TAT      1104
Trp Ile Pro Pro Ala Asp Thr Gly Gly Arg Lys Asp Val Ser Tyr Tyr
        355                 360                 365

ATT GCA TGC AAG AAG TGC AAC TCC CAT GCA GGT GTG TGT GAG GAG TGT      1152
Ile Ala Cys Lys Lys Cys Asn Ser His Ala Gly Val Cys Glu Glu Cys
    370                 375                 380

GGC GGT CAT GTC AGG TAC CTT CCC CGG CAA AGC GGC CTG AAA AAC ACC      1200
Gly Gly His Val Arg Tyr Leu Pro Arg Gln Ser Gly Leu Lys Asn Thr
385                 390                 395                 400

TCT GTC ATG ATG GTG GAT CTA CTC GCT CAC ACA AAC TAT ACC TTT GAG      1248
Ser Val Met Met Val Asp Leu Leu Ala His Thr Asn Tyr Thr Phe Glu
                405                 410                 415

ATT GAG GCA GTG AAT GGA GTG TCC GAC TTG AGC CCA GGA GCC CGG CAG      1296
Ile Glu Ala Val Asn Gly Val Ser Asp Leu Ser Pro Gly Ala Arg Gln
            420                 425                 430

TAT GTG TCT GTA AAT GTA ACC ACA AAT CAA GCA GCT CCA TCT CCA GTC      1344
Tyr Val Ser Val Asn Val Thr Thr Asn Gln Ala Ala Pro Ser Pro Val
        435                 440                 445

ACC AAT GTG AAA AAA GGG AAA ATT GCA AAA AAC AGC ATC TCT TTG TCT      1392
Thr Asn Val Lys Lys Gly Lys Ile Ala Lys Asn Ser Ile Ser Leu Ser
    450                 455                 460

TGG CAA GAA CCA GAT CGT CCC AAT GGA ATC ATC CTA GAG TAT GAA ATC      1440
Trp Gln Glu Pro Asp Arg Pro Asn Gly Ile Ile Leu Glu Tyr Glu Ile
465                 470                 475                 480

AAG CAT TTT GAA AAG GAC CAA GAG ACC AGC TAC ACG ATT ATC AAA TCT      1488
Lys His Phe Glu Lys Asp Gln Glu Thr Ser Tyr Thr Ile Ile Lys Ser
                485                 490                 495

AAA GAG ACA ACT ATT ACT GCA GAG GGC TTG AAA CCA GCT TCA GTT TAT      1536
Lys Glu Thr Thr Ile Thr Ala Glu Gly Leu Lys Pro Ala Ser Val Tyr
            500                 505                 510

GTC TTC CAA ATT CGA GCA CGT ACA GCA GCA GGC TAT GGT GTC TTC AGT      1584
Val Phe Gln Ile Arg Ala Arg Thr Ala Ala Gly Tyr Gly Val Phe Ser
        515                 520                 525

CGA AGA TTT GAG TTT GAA ACC ACC CCA GTG TTT GCA GCA TCC AGC GAT      1632
Arg Arg Phe Glu Phe Glu Thr Thr Pro Val Phe Ala Ala Ser Ser Asp
    530                 535                 540
```

```
CAA AGC CAG ATT CCT GTA ATT GCT GTG TCT GTG ACA GTA GGA GTC ATT      1680
Gln Ser Gln Ile Pro Val Ile Ala Val Ser Val Thr Val Gly Val Ile
545                 550                 555                 560

TTG TTG GCA GTG GTT ATC GGC GTC CTC CTC AGT GGA AGG CGG TGT GGC      1728
Leu Leu Ala Val Val Ile Gly Val Leu Leu Ser Gly Arg Arg Cys Gly
                565                 570                 575

TAC AGC AAA GCA AAA CAA GAT CCA GAA GAG GAA AAG ATG CAT TTT CAT      1776
Tyr Ser Lys Ala Lys Gln Asp Pro Glu Glu Glu Lys Met His Phe His
            580                 585                 590

AAT GGG CAC ATT AAA CTG CCA GGA GTA AGA ACT TAC ATT GAT CCA CAT      1824
Asn Gly His Ile Lys Leu Pro Gly Val Arg Thr Tyr Ile Asp Pro His
        595                 600                 605

ACC TAT GAG GAT CCC AAT CAA GCT GTC CAC GAA TTT GCC AAG GAG ATA      1872
Thr Tyr Glu Asp Pro Asn Gln Ala Val His Glu Phe Ala Lys Glu Ile
    610                 615                 620

GAA GCA TCA TGT ATC ACC ATT GAG AGA GTT ATT GGA GCA GGT GAA TTT      1920
Glu Ala Ser Cys Ile Thr Ile Glu Arg Val Ile Gly Ala Gly Glu Phe
625                 630                 635                 640

GGT GAA GTT TGT AGT GGA CGT TTG AAA CTA CCA GGA AAA AGA GAA TTA      1968
Gly Glu Val Cys Ser Gly Arg Leu Lys Leu Pro Gly Lys Arg Glu Leu
                645                 650                 655

CCT GTG GCT ATC AAA ACC CTT AAA GTA GGC TAT ACT GAA AAG CAA CGC      2016
Pro Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr Glu Lys Gln Arg
            660                 665                 670

AGA GAT TTC CTA GGT GAA GCA AGT ATC ATG GGA CAG TTT GAT CAT CCT      2064
Arg Asp Phe Leu Gly Glu Ala Ser Ile Met Gly Gln Phe Asp His Pro
        675                 680                 685

AAC ATC ATC CAT TTA GAA GGT GTG GTG ACC AAA AGT AAA CCA GTG ATG      2112
Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Ser Lys Pro Val Met
    690                 695                 700

ATC GTG ACA GAG TAT ATG GAG AAT GGC TCT TTA GAT ACA TTT TTG AAG      2160
Ile Val Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp Thr Phe Leu Lys
705                 710                 715                 720

AAA AAC GAT GGG CAG TTC ACT GTG ATT CAG CTT GTT GGC ATG CTG AGA      2208
Lys Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met Leu Arg
                725                 730                 735

GGT ATC TCT GCA GGA ATG AAG TAC CTT TCT GAC ATG GGC TAT GTG CAT      2256
Gly Ile Ser Ala Gly Met Lys Tyr Leu Ser Asp Met Gly Tyr Val His
            740                 745                 750

AGA GAT CTT GCT GCC AGA AAC ATC TTA ATC AAC AGT AAC CTT GTG TGC      2304
Arg Asp Leu Ala Ala Arg Asn Ile Leu Ile Asn Ser Asn Leu Val Cys
        755                 760                 765
```

```
AAA GTG TCT GAC TTT GGA CTT TCC CGG GTA CTG GAA GAT GAT CCC GAG      2352
Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp Pro Glu
    770                 775                 780

GCA GCC TAC ACC ACA AGG GGA GGA AAA ATT CCA ATC AGA TGG ACT GCC      2400
Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala
785                 790                 795                 800

CCA GAA GCA ATA GCT TTC CGA AAG TTT ACT TCT GCC AGT GAT GTC TGG      2448
Pro Glu Ala Ile Ala Phe Arg Lys Phe Thr Ser Ala Ser Asp Val Trp
                805                 810                 815

AGT TAT GGA ATA GTA ATG TGG GAA GTT GTG TCT TAT GGA GAG AGA CCC      2496
Ser Tyr Gly Ile Val Met Trp Glu Val Val Ser Tyr Gly Glu Arg Pro
            820                 825                 830

TAC TGG GAG ATG ACC AAT CAA GAT GTG ATT AAA GCG GTA GAG GAA GGC      2544
Tyr Trp Glu Met Thr Asn Gln Asp Val Ile Lys Ala Val Glu Glu Gly
        835                 840                 845

TAT CGT CTG CCA AGC CCC ATG GAT TGT CCT GCT GCT CTC TAT CAG TTA      2592
Tyr Arg Leu Pro Ser Pro Met Asp Cys Pro Ala Ala Leu Tyr Gln Leu
    850                 855                 860

ATG CTG GAT TGC TGG CAG AAA GAG CGA AAT AGC AGG CCC AAG TTT GAT      2640
Met Leu Asp Cys Trp Gln Lys Glu Arg Asn Ser Arg Pro Lys Phe Asp
865                 870                 875                 880

GAA ATA GTC AAC ATG TTG GAC AAG CTG ATA CGT AAC CCA AGT AGT CTG      2688
Glu Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro Ser Ser Leu
                885                 890                 895

AAG ACG CTG GTT AAT GCA TCC TGC AGA GTA TCT AAT TTA TTG GCA GAA      2736
Lys Thr Leu Val Asn Ala Ser Cys Arg Val Ser Asn Leu Leu Ala Glu
            900                 905                 910

CAT AGC CCA CTA GGA TCT GGG GCC TAC AGA TCA GTA GGT GAA TGG CTA      2784
His Ser Pro Leu Gly Ser Gly Ala Tyr Arg Ser Val Gly Glu Trp Leu
        915                 920                 925

GAG GCA ATC AAG ATG GGC CGG TAT ACA GAG ATT TTC ATG GAA AAT GGA      2832
Glu Ala Ile Lys Met Gly Arg Tyr Thr Glu Ile Phe Met Glu Asn Gly
    930                 935                 940

TAC AGT TCA ATG GAC GCT GTG GCT CAG GTG ACC TTG GAG GAT TTG AGA      2880
Tyr Ser Ser Met Asp Ala Val Ala Gln Val Thr Leu Glu Asp Leu Arg
945                 950                 955                 960

CGG CTT GGA GTG ACT CTT GTC GGT CAC CAG AAG AAG ATC ATG AAC AGC      2928
Arg Leu Gly Val Thr Leu Val Gly His Gln Lys Lys Ile Met Asn Ser
                965                 970                 975

CTT CAA GAA ATG AAG GTG CAG CTG GTA AAC GGA ATG GTG CCA TTG TAACTTCATG
2983
Leu Gln Glu Met Lys Val Gln Leu Val Asn Gly Met Val Pro Leu
            980                 985                 990

TAAATGTCGC TTCTTCAAGT GAATGATTCT GCACTTTGTA AACAGCACTG AGATTTATTT    3043
```

TAACAAAAAA AGGGGGAAAA GGGAAAACAG TGATTTCTAA ACCTTAGAAA ACATTTGCCT 3103

CAGCCACAGA ATTTGTAATC ATGGTTTTAC TGAAGTATCC AGTTCTTAGT CCTTAGTCT 3162

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 991 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```
Pro Ala Ser Leu Ala Gly Cys Tyr Ser Ala Pro Arg Arg Ala Pro Leu
 1               5                  10                  15

Trp Thr Cys Leu Leu Leu Cys Ala Ala Leu Arg Thr Leu Leu Ala Ser
            20                  25                  30

Pro Ser Asn Glu Val Asn Leu Leu Asp Ser Arg Thr Val Met Gly Asp
        35                  40                  45

Leu Gly Trp Ile Ala Phe Pro Lys Asn Gly Trp Glu Glu Ile Gly Glu
    50                  55                  60

Val Asp Glu Asn Tyr Ala Pro Ile His Thr Tyr Gln Val Cys Lys Val
65                  70                  75                  80

Met Glu Gln Asn Gln Asn Asn Trp Leu Leu Thr Ser Trp Ile Ser Asn
                85                  90                  95

Glu Gly Ala Ser Arg Ile Phe Ile Glu Leu Lys Phe Thr Leu Arg Asp
            100                 105                 110

Cys Asn Ser Leu Pro Gly Gly Leu Gly Thr Cys Lys Glu Thr Phe Asn
        115                 120                 125

Met Tyr Tyr Phe Glu Ser Asp Asp Gln Asn Gly Arg Asn Ile Lys Glu
    130                 135                 140

Asn Gln Tyr Ile Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr
145                 150                 155                 160

Glu Leu Asp Leu Gly Asp Arg Val Met Lys Leu Asn Thr Glu Val Arg
                165                 170                 175

Asp Val Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp
            180                 185                 190

Val Gly Ala Cys Ile Ala Leu Val Ser Val Arg Val Tyr Tyr Lys Lys
        195                 200                 205

Cys Pro Ser Val Val Arg His Leu Ala Val Phe Pro Asp Thr Ile Thr
    210                 215                 220
```

```
Gly Ala Asp Ser Ser Gln Leu Leu Glu Val Ser Gly Ser Cys Val Asn
225                 230                 235                 240

His Ser Val Thr Asp Glu Pro Pro Lys Met His Cys Ser Ala Glu Gly
                245                 250                 255

Glu Trp Leu Val Pro Ile Gly Lys Cys Met Cys Lys Ala Gly Tyr Glu
            260                 265                 270

Glu Lys Asn Gly Thr Cys Gln Val Cys Arg Pro Gly Phe Phe Lys Ala
        275                 280                 285

Ser Pro His Ile Gln Ser Cys Gly Lys Cys Pro Pro His Ser Tyr Thr
    290                 295                 300

His Glu Glu Ala Ser Thr Ser Cys Val Cys Glu Lys Asp Tyr Phe Arg
305                 310                 315                 320

Arg Glu Ser Asp Pro Pro Thr Met Ala Cys Thr Arg Pro Pro Ser Ala
                325                 330                 335

Pro Arg Asn Ala Ile Ser Asn Val Asn Glu Thr Ser Val Phe Leu Glu
            340                 345                 350

Trp Ile Pro Pro Ala Asp Thr Gly Gly Arg Lys Asp Val Ser Tyr Tyr
        355                 360                 365

Ile Ala Cys Lys Lys Cys Asn Ser His Ala Gly Val Cys Glu Glu Cys
    370                 375                 380

Gly Gly His Val Arg Tyr Leu Pro Arg Gln Ser Gly Leu Lys Asn Thr
385                 390                 395                 400

Ser Val Met Met Val Asp Leu Leu Ala His Thr Asn Tyr Thr Phe Glu
                405                 410                 415

Ile Glu Ala Val Asn Gly Val Ser Asp Leu Ser Pro Gly Ala Arg Gln
            420                 425                 430

Tyr Val Ser Val Asn Val Thr Thr Asn Gln Ala Ala Pro Ser Pro Val
        435                 440                 445

Thr Asn Val Lys Lys Gly Lys Ile Ala Lys Asn Ser Ile Ser Leu Ser
    450                 455                 460

Trp Gln Glu Pro Asp Arg Pro Asn Gly Ile Ile Leu Glu Tyr Glu Ile
465                 470                 475                 480

Lys His Phe Glu Lys Asp Gln Glu Thr Ser Tyr Thr Ile Ile Lys Ser
                485                 490                 495

Lys Glu Thr Thr Ile Thr Ala Glu Gly Leu Lys Pro Ala Ser Val Tyr
            500                 505                 510

Val Phe Gln Ile Arg Ala Arg Thr Ala Ala Gly Tyr Gly Val Phe Ser
        515                 520                 525
```

```
Arg Arg Phe Glu Phe Glu Thr Thr Pro Val Phe Ala Ala Ser Ser Asp
    530                 535                 540

Gln Ser Gln Ile Pro Val Ile Ala Val Ser Val Thr Val Gly Val Ile
545                 550                 555                 560

Leu Leu Ala Val Val Ile Gly Val Leu Leu Ser Gly Arg Arg Cys Gly
                565                 570                 575

Tyr Ser Lys Ala Lys Gln Asp Pro Glu Glu Glu Lys Met His Phe His
            580                 585                 590

Asn Gly His Ile Lys Leu Pro Gly Val Arg Thr Tyr Ile Asp Pro His
        595                 600                 605

Thr Tyr Glu Asp Pro Asn Gln Ala Val His Glu Phe Ala Lys Glu Ile
    610                 615                 620

Glu Ala Ser Cys Ile Thr Ile Glu Arg Val Ile Gly Ala Gly Glu Phe
625                 630                 635                 640

Gly Glu Val Cys Ser Gly Arg Leu Lys Leu Pro Gly Lys Arg Glu Leu
                645                 650                 655

Pro Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr Glu Lys Gln Arg
            660                 665                 670

Arg Asp Phe Leu Gly Glu Ala Ser Ile Met Gly Gln Phe Asp His Pro
        675                 680                 685

Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Ser Lys Pro Val Met
    690                 695                 700

Ile Val Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp Thr Phe Leu Lys
705                 710                 715                 720

Lys Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met Leu Arg
                725                 730                 735

Gly Ile Ser Ala Gly Met Lys Tyr Leu Ser Asp Met Gly Tyr Val His
            740                 745                 750

Arg Asp Leu Ala Ala Arg Asn Ile Leu Ile Asn Ser Asn Leu Val Cys
        755                 760                 765

Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp Pro Glu
    770                 775                 780

Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala
785                 790                 795                 800

Pro Glu Ala Ile Ala Phe Arg Lys Phe Thr Ser Ala Ser Asp Val Trp
                805                 810                 815

Ser Tyr Gly Ile Val Met Trp Glu Val Val Ser Tyr Gly Glu Arg Pro
            820                 825                 830
```

```
Tyr Trp Glu Met Thr Asn Gln Asp Val Ile Lys Ala Val Glu Glu Gly
        835                 840                 845

Tyr Arg Leu Pro Ser Pro Met Asp Cys Pro Ala Ala Leu Tyr Gln Leu
    850                 855                 860

Met Leu Asp Cys Trp Gln Lys Glu Arg Asn Ser Arg Pro Lys Phe Asp
865                 870                 875                 880

Glu Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro Ser Ser Leu
                885                 890                 895

Lys Thr Leu Val Asn Ala Ser Cys Arg Val Ser Asn Leu Leu Ala Glu
            900                 905                 910

His Ser Pro Leu Gly Ser Gly Ala Tyr Arg Ser Val Gly Glu Trp Leu
        915                 920                 925

Glu Ala Ile Lys Met Gly Arg Tyr Thr Glu Ile Phe Met Glu Asn Gly
    930                 935                 940

Tyr Ser Ser Met Asp Ala Val Ala Gln Val Thr Leu Glu Asp Leu Arg
945                 950                 955                 960

Arg Leu Gly Val Thr Leu Val Gly His Gln Lys Lys Ile Met Asn Ser
                965                 970                 975

Leu Gln Glu Met Lys Val Gln Leu Val Asn Gly Met Val Pro Leu
            980                 985                 990
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3116 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 34..2994

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

```
AAGCGGCAGG AGCAGCGTTG GCACCGGCGA ACC ATG GCT GGG ATT TTC TAT TTC      54
                                      Met Ala Gly Ile Phe Tyr Phe
                                        1               5

GCC CTA TTT TCG TGT CTC TTC GGG ATT TGC GAC GCT GTC ACA GGT TCC      102
Ala Leu Phe Ser Cys Leu Phe Gly Ile Cys Asp Ala Val Thr Gly Ser
         10                  15                  20
```

```
AGG GTA TAC CCC GCG AAT GAA GTT ACC TTA TTG GAT TCC AGA TCT GTT        150
Arg Val Tyr Pro Ala Asn Glu Val Thr Leu Leu Asp Ser Arg Ser Val
     25                  30                  35

CAG GGA GAA CTT GGG TGG ATA GCA AGC CCT CTG GAA GGA GGG TGG GAG        198
Gln Gly Glu Leu Gly Trp Ile Ala Ser Pro Leu Glu Gly Gly Trp Glu
 40                  45                  50                  55

GAA GTG AGT ATC ATG GAT GAA AAA AAT ACA CCA ATC CGA ACC TAC CAA        246
Glu Val Ser Ile Met Asp Glu Lys Asn Thr Pro Ile Arg Thr Tyr Gln
                 60                  65                  70

GTG TGC AAT GTG ATG GAA CCC AGC CAG AAT AAC TGG CTA CGA ACT GAT        294
Val Cys Asn Val Met Glu Pro Ser Gln Asn Asn Trp Leu Arg Thr Asp
             75                  80                  85

TGG ATC ACC CGA GAA GGG GCT CAG AGG GTG TAT ATT GAG ATT AAA TTC        342
Trp Ile Thr Arg Glu Gly Ala Gln Arg Val Tyr Ile Glu Ile Lys Phe
         90                  95                 100

ACC TTG AGG GAC TGC AAT AGT CTT CCG GGC GTC ATG GGG ACT TGC AAG        390
Thr Leu Arg Asp Cys Asn Ser Leu Pro Gly Val Met Gly Thr Cys Lys
    105                 110                 115

GAG ACG TTT AAC CTG TAC TAC TAT GAA TCA GAC AAC GAC AAA GAG CGT        438
Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu Ser Asp Asn Asp Lys Glu Arg
120                 125                 130                 135

TTC ATC AGA GAG AAC CAG TTT GTC AAA ATT GAC ACC ATT GCT GCT GAT        486
Phe Ile Arg Glu Asn Gln Phe Val Lys Ile Asp Thr Ile Ala Ala Asp
                140                 145                 150

GAG AGC TTC ACC CAA GTG GAC ATT GGT GAC AGA ATC ATG AAG CTG AAC        534
Glu Ser Phe Thr Gln Val Asp Ile Gly Asp Arg Ile Met Lys Leu Asn
            155                 160                 165

ACC GAG ATC CGG GAT GTA GGG CCA TTA AGC AAA AAG GGG TTT TAC CTG        582
Thr Glu Ile Arg Asp Val Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu
        170                 175                 180

GCT TTT CAG GAT GTG GGG GCC TGC ATC GCC CTG GTA TCA GTC CGT GTG        630
Ala Phe Gln Asp Val Gly Ala Cys Ile Ala Leu Val Ser Val Arg Val
    185                 190                 195

TTC TAT AAA AAG TGT CCA CTC ACA GTC CGC AAT CTG GCC CAG TTT CCT        678
Phe Tyr Lys Lys Cys Pro Leu Thr Val Arg Asn Leu Ala Gln Phe Pro
200                 205                 210                 215

GAC ACC ATC ACA GGG GCT GAT ACG TCT TCC CTG GTG GAA GTT CGA GGC        726
Asp Thr Ile Thr Gly Ala Asp Thr Ser Ser Leu Val Glu Val Arg Gly
                220                 225                 230

TCC TGT GTC AAC AAC TCA GAA GAG AAA GAT GTG CCA AAA ATG TAC TGT        774
Ser Cys Val Asn Asn Ser Glu Glu Lys Asp Val Pro Lys Met Tyr Cys
            235                 240                 245
```

```
GGG GCA GAT GGT GAA TGG CTG GTA CCC ATT GGC AAC TGC CTA TGC AAC        822
Gly Ala Asp Gly Glu Trp Leu Val Pro Ile Gly Asn Cys Leu Cys Asn
        250                 255                 260

GCT GGG CAT GAG GAG CGG AGC GGA GAA TGC CAA GCT TGC AAA ATT GGA        870
Ala Gly His Glu Glu Arg Ser Gly Glu Cys Gln Ala Cys Lys Ile Gly
    265                 270                 275

TAT TAC AAG GCT CTC TCC ACG GAT GCC ACC TGT GCC AAG TGC CCA CCC        918
Tyr Tyr Lys Ala Leu Ser Thr Asp Ala Thr Cys Ala Lys Cys Pro Pro
280                 285                 290                 295

CAC AGC TAC TCT GTC TGG GAA GGA GCC ACC TCG TGC ACC TGT GAC CGA        966
His Ser Tyr Ser Val Trp Glu Gly Ala Thr Ser Cys Thr Cys Asp Arg
                300                 305                 310

GGC TTT TTC AGA GCT GAC AAC GAT GCT GCC TCT ATG CCC TGC ACC CGT       1014
Gly Phe Phe Arg Ala Asp Asn Asp Ala Ala Ser Met Pro Cys Thr Arg
            315                 320                 325

CCA CCA TCT GCT CCC CTG AAC TTG ATT TCA AAT GTC AAC GAG ACA TCT       1062
Pro Pro Ser Ala Pro Leu Asn Leu Ile Ser Asn Val Asn Glu Thr Ser
        330                 335                 340

GTG AAC TTG GAA TGG AGT AGC CCT CAG AAT ACA GGT GGC CGC CAG GAC       1110
Val Asn Leu Glu Trp Ser Ser Pro Gln Asn Thr Gly Gly Arg Gln Asp
    345                 350                 355

ATT TCC TAT AAT GTG GTA TGC AAG AAA TGT GGA GCT GGT GAC CCC AGC       1158
Ile Ser Tyr Asn Val Val Cys Lys Lys Cys Gly Ala Gly Asp Pro Ser
360                 365                 370                 375

AAG TGC CGA CCC TGT GGA AGT GGG GTC CAC TAC ACC CCA CAG CAG AAT       1206
Lys Cys Arg Pro Cys Gly Ser Gly Val His Tyr Thr Pro Gln Gln Asn
                380                 385                 390

GGC TTG AAG ACC ACC AAA GTC TCC ATC ACT GAC CTC CTA GCT CAT ACC       1254
Gly Leu Lys Thr Thr Lys Val Ser Ile Thr Asp Leu Leu Ala His Thr
            395                 400                 405

AAT TAC ACC TTT GAA ATC TGG GCT GTG AAT GGA GTG TCC AAA TAT AAC       1302
Asn Tyr Thr Phe Glu Ile Trp Ala Val Asn Gly Val Ser Lys Tyr Asn
        410                 415                 420

CCT AAC CCA GAC CAA TCA GTT TCT GTC ACT GTG ACC ACC AAC CAA GCA       1350
Pro Asn Pro Asp Gln Ser Val Ser Val Thr Val Thr Thr Asn Gln Ala
    425                 430                 435

GCA CCA TCA TCC ATT GCT TTG GTC CAG GCT AAA GAA GTC ACA AGA TAC       1398
Ala Pro Ser Ser Ile Ala Leu Val Gln Ala Lys Glu Val Thr Arg Tyr
440                 445                 450                 455

AGT GTG GCA CTG GCT TGG CTG GAA CCA GAT CGG CCC AAT GGG GTA ATC       1446
Ser Val Ala Leu Ala Trp Leu Glu Pro Asp Arg Pro Asn Gly Val Ile
                460                 465                 470
```

```
CTG GAA TAT GAA GTC AAG TAT TAT GAG AAG GAT CAG AAT GAG CGA AGC      1494
Leu Glu Tyr Glu Val Lys Tyr Tyr Glu Lys Asp Gln Asn Glu Arg Ser
            475                 480                 485

TAT CGT ATA GTT CGG ACA GCT GCC AGG AAC ACA GAT ATC AAA GGC CTG      1542
Tyr Arg Ile Val Arg Thr Ala Ala Arg Asn Thr Asp Ile Lys Gly Leu
        490                 495                 500

AAC CCT CTC ACT TCC TAT GTT TTC CAC GTG CGA GCC AGG ACA GCA GCT      1590
Asn Pro Leu Thr Ser Tyr Val Phe His Val Arg Ala Arg Thr Ala Ala
    505                 510                 515

GGC TAT GGA GAC TTC AGT GAG CCC TTG GAG GTT ACA ACC AAC ACA GTG      1638
Gly Tyr Gly Asp Phe Ser Glu Pro Leu Glu Val Thr Thr Asn Thr Val
520                 525                 530                 535

CCT TCC CGG ATC ATT GGA GAT GGG GCT AAC TCC ACA GTC CTT CTG GTC      1686
Pro Ser Arg Ile Ile Gly Asp Gly Ala Asn Ser Thr Val Leu Leu Val
                540                 545                 550

TCT GTC TCG GGC AGT GTG GTG CTG GTG GTA ATT CTC ATT GCA GCT TTT      1734
Ser Val Ser Gly Ser Val Val Leu Val Val Ile Leu Ile Ala Ala Phe
            555                 560                 565

GTC ATC AGC CGG AGA CGG AGT AAA TAC AGT AAA GCC AAA CAA GAA GCG      1782
Val Ile Ser Arg Arg Arg Ser Lys Tyr Ser Lys Ala Lys Gln Glu Ala
        570                 575                 580

GAT GAA GAG AAA CAT TTG AAT CAA GGT GTA AGA ACA TAT GTG GAC CCC      1830
Asp Glu Glu Lys His Leu Asn Gln Gly Val Arg Thr Tyr Val Asp Pro
    585                 590                 595

TTT ACG TAC GAA GAT CCC AAC CAA GCA GTG CGA GAG TTT GCC AAA GAA      1878
Phe Thr Tyr Glu Asp Pro Asn Gln Ala Val Arg Glu Phe Ala Lys Glu
600                 605                 610                 615

ATT GAC GCA TCC TGC ATT AAG ATT GAA AAA GTT ATA GGA GTT GGT GAA      1926
Ile Asp Ala Ser Cys Ile Lys Ile Glu Lys Val Ile Gly Val Gly Glu
                620                 625                 630

TTT GGT GAG GTA TGC AGT GGG CGT CTC AAA GTG CCT GGC AAG AGA GAG      1974
Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Val Pro Gly Lys Arg Glu
            635                 640                 645

ATC TGT GTG GCT ATC AAG ACT CTG AAA GCT GGT TAT ACA GAC AAA CAG      2022
Ile Cys Val Ala Ile Lys Thr Leu Lys Ala Gly Tyr Thr Asp Lys Gln
        650                 655                 660

AGG AGA GAC TTC CTG AGT GAG GCC AGC ATC ATG GGA CAG TTT GAC CAT      2070
Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met Gly Gln Phe Asp His
    665                 670                 675

CCG AAC ATC ATT CAC TTG GAA GGC GTG GTC ACT AAA TGT AAA CCA GTA      2118
Pro Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Cys Lys Pro Val
680                 685                 690                 695
```

```
ATG ATC ATA ACA GAG TAC ATG GAG AAT GGC TCC TTG GAT GCA TTC CTC      2166
Met Ile Ile Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp Ala Phe Leu
                700                 705                 710

AGG AAA AAT GAT GGC AGA TTT ACA GTC ATT CAG CTG GTG GGC ATG CTT      2214
Arg Lys Asn Asp Gly Arg Phe Thr Val Ile Gln Leu Val Gly Met Leu
            715                 720                 725

CGT GGC ATT GGG TCT GGG ATG AAG TAT TTA TCT GAT ATG AGC TAT GTG      2262
Arg Gly Ile Gly Ser Gly Met Lys Tyr Leu Ser Asp Met Ser Tyr Val
        730                 735                 740

CAT CGT GAT CTG GCC GCA CGG AAC ATC CTG GTG AAC AGC AAC TTG GTC      2310
His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val
    745                 750                 755

TGC AAA GTG TCT GAT TTT GGC ATG TCC CGA GTG CTT GAG GAT GAT CCG      2358
Cys Lys Val Ser Asp Phe Gly Met Ser Arg Val Leu Glu Asp Asp Pro
760                 765                 770                 775

GAA GCA GCT TAC ACC ACC AGG GGT GGC AAG ATT CCT ATC CGG TGG ACT      2406
Glu Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr
                780                 785                 790

GCG CCA GAA GCA ATT GCC TAT CGT AAA TTC ACA TCA GCA AGT GAT GTA      2454
Ala Pro Glu Ala Ile Ala Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val
            795                 800                 805

TGG AGC TAT GGA ATC GTT ATG TGG GAA GTG ATG TCG TAC GGG GAG AGG      2502
Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met Ser Tyr Gly Glu Arg
        810                 815                 820

CCC TAT TGG GAT ATG TCC AAT CAA GAT GTG ATT AAA GCC ATT GAG GAA      2550
Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile Lys Ala Ile Glu Glu
    825                 830                 835

GGC TAT CGG TTA CCC CCT CCA ATG GAC TGC CCC ATT GCG CTC CAC CAG      2598
Gly Tyr Arg Leu Pro Pro Pro Met Asp Cys Pro Ile Ala Leu His Gln
840                 845                 850                 855

CTG ATG CTA GAC TGC TGG CAG AAG GAG AGG AGC GAC AGG CCT AAA TTT      2646
Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ser Asp Arg Pro Lys Phe
                860                 865                 870

GGG CAG ATT GTC AAC ATG TTG GAC AAA CTC ATC CGC AAC CCC AAC AGC      2694
Gly Gln Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro Asn Ser
            875                 880                 885

TTG AAG AGG ACA GGG ACG GAG AGC TCC AGA CCT AAC ACT GCC TTG TTG      2742
Leu Lys Arg Thr Gly Thr Glu Ser Ser Arg Pro Asn Thr Ala Leu Leu
        890                 895                 900

GAT CCA AGC TCC CCT GAA TTC TCT GCT GTG GTA TCA GTG GGC GAT TGG      2790
Asp Pro Ser Ser Pro Glu Phe Ser Ala Val Val Ser Val Gly Asp Trp
    905                 910                 915
```

```
CTC CAG GCC ATT AAA ATG GAC CGG TAT AAG GAT AAC TTC ACA GCT GCT      2838
Leu Gln Ala Ile Lys Met Asp Arg Tyr Lys Asp Asn Phe Thr Ala Ala
920                 925                 930                 935

GGT TAT ACC ACA CTA GAG GCT GTG GTG CAC GTG AAC CAG GAG GAC CTG      2886
Gly Tyr Thr Thr Leu Glu Ala Val Val His Val Asn Gln Glu Asp Leu
                940                 945                 950

GCA AGA ATT GGT ATC ACA GCC ATC ACG CAC CAG AAT AAG ATT TTG AGC      2934
Ala Arg Ile Gly Ile Thr Ala Ile Thr His Gln Asn Lys Ile Leu Ser
            955                 960                 965

AGT GTC CAG GCA ATG CGA ACC CAA ATG CAG CAG ATG CAC GGC AGA ATG      2982
Ser Val Gln Ala Met Arg Thr Gln Met Gln Gln Met His Gly Arg Met
        970                 975                 980

GTT CCC GTC TGAGCCAGTA CTGAATAAAC TCAAAACTCT TGAAATTAGT              3031
Val Pro Val
    985

TTACCTCATC CATGCACTTT AATTGAAGAA CTGCACTTTT TTTACTTCGT CTTCGCCCTC    3091

TGAAATTAAA GAAATGAAAA AAAAA                                          3116
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 986 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
Met Ala Gly Ile Phe Tyr Phe Ala Leu Phe Ser Cys Leu Phe Gly Ile
  1               5                  10                  15

Cys Asp Ala Val Thr Gly Ser Arg Val Tyr Pro Ala Asn Glu Val Thr
            20                  25                  30

Leu Leu Asp Ser Arg Ser Val Gln Gly Glu Leu Gly Trp Ile Ala Ser
        35                  40                  45

Pro Leu Glu Gly Gly Trp Glu Glu Val Ser Ile Met Asp Glu Lys Asn
    50                  55                  60

Thr Pro Ile Arg Thr Tyr Gln Val Cys Asn Val Met Glu Pro Ser Gln
65                  70                  75                  80

Asn Asn Trp Leu Arg Thr Asp Trp Ile Thr Arg Glu Gly Ala Gln Arg
                85                  90                  95

Val Tyr Ile Glu Ile Lys Phe Thr Leu Arg Asp Cys Asn Ser Leu Pro
            100                 105                 110
```

```
Gly Val Met Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu
        115                 120                 125

Ser Asp Asn Asp Lys Glu Arg Phe Ile Arg Glu Asn Gln Phe Val Lys
    130                 135                 140

Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Val Asp Ile Gly
145                 150                 155                 160

Asp Arg Ile Met Lys Leu Asn Thr Glu Ile Arg Asp Val Gly Pro Leu
                165                 170                 175

Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Ile
            180                 185                 190

Ala Leu Val Ser Val Arg Val Phe Tyr Lys Lys Cys Pro Leu Thr Val
        195                 200                 205

Arg Asn Leu Ala Gln Phe Pro Asp Thr Ile Thr Gly Ala Asp Thr Ser
    210                 215                 220

Ser Leu Val Glu Val Arg Gly Ser Cys Val Asn Asn Ser Glu Glu Lys
225                 230                 235                 240

Asp Val Pro Lys Met Tyr Cys Gly Ala Asp Gly Glu Trp Leu Val Pro
                245                 250                 255

Ile Gly Asn Cys Leu Cys Asn Ala Gly His Glu Glu Arg Ser Gly Glu
            260                 265                 270

Cys Gln Ala Cys Lys Ile Gly Tyr Tyr Lys Ala Leu Ser Thr Asp Ala
        275                 280                 285

Thr Cys Ala Lys Cys Pro Pro His Ser Tyr Ser Val Trp Glu Gly Ala
    290                 295                 300

Thr Ser Cys Thr Cys Asp Arg Gly Phe Phe Arg Ala Asp Asn Asp Ala
305                 310                 315                 320

Ala Ser Met Pro Cys Thr Arg Pro Pro Ser Ala Pro Leu Asn Leu Ile
                325                 330                 335

Ser Asn Val Asn Glu Thr Ser Val Asn Leu Glu Trp Ser Ser Pro Gln
            340                 345                 350

Asn Thr Gly Gly Arg Gln Asp Ile Ser Tyr Asn Val Val Cys Lys Lys
        355                 360                 365

Cys Gly Ala Gly Asp Pro Ser Lys Cys Arg Pro Cys Gly Ser Gly Val
    370                 375                 380

His Tyr Thr Pro Gln Gln Asn Gly Leu Lys Thr Thr Lys Val Ser Ile
385                 390                 395                 400

Thr Asp Leu Leu Ala His Thr Asn Tyr Thr Phe Glu Ile Trp Ala Val
                405                 410                 415
```

```
Asn Gly Val Ser Lys Tyr Asn Pro Asn Pro Asp Gln Ser Val Ser Val
            420                 425                 430

Thr Val Thr Thr Asn Gln Ala Ala Pro Ser Ser Ile Ala Leu Val Gln
        435                 440                 445

Ala Lys Glu Val Thr Arg Tyr Ser Val Ala Leu Ala Trp Leu Glu Pro
    450                 455                 460

Asp Arg Pro Asn Gly Val Ile Leu Glu Tyr Glu Val Lys Tyr Tyr Glu
465                 470                 475                 480

Lys Asp Gln Asn Glu Arg Ser Tyr Arg Ile Val Arg Thr Ala Ala Arg
                485                 490                 495

Asn Thr Asp Ile Lys Gly Leu Asn Pro Leu Thr Ser Tyr Val Phe His
            500                 505                 510

Val Arg Ala Arg Thr Ala Ala Gly Tyr Gly Asp Phe Ser Glu Pro Leu
        515                 520                 525

Glu Val Thr Thr Asn Thr Val Pro Ser Arg Ile Ile Gly Asp Gly Ala
    530                 535                 540

Asn Ser Thr Val Leu Leu Val Ser Val Ser Gly Ser Val Val Leu Val
545                 550                 555                 560

Val Ile Leu Ile Ala Ala Phe Val Ile Ser Arg Arg Arg Ser Lys Tyr
                565                 570                 575

Ser Lys Ala Lys Gln Glu Ala Asp Glu Glu Lys His Leu Asn Gln Gly
            580                 585                 590

Val Arg Thr Tyr Val Asp Pro Phe Thr Tyr Glu Asp Pro Asn Gln Ala
        595                 600                 605

Val Arg Glu Phe Ala Lys Glu Ile Asp Ala Ser Cys Ile Lys Ile Glu
    610                 615                 620

Lys Val Ile Gly Val Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu
625                 630                 635                 640

Lys Val Pro Gly Lys Arg Glu Ile Cys Val Ala Ile Lys Thr Leu Lys
                645                 650                 655

Ala Gly Tyr Thr Asp Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser
            660                 665                 670

Ile Met Gly Gln Phe Asp His Pro Asn Ile Ile His Leu Glu Gly Val
        675                 680                 685

Val Thr Lys Cys Lys Pro Val Met Ile Ile Thr Glu Tyr Met Glu Asn
    690                 695                 700

Gly Ser Leu Asp Ala Phe Leu Arg Lys Asn Asp Gly Arg Phe Thr Val
705                 710                 715                 720
```

```
Ile Gln Leu Val Gly Met Leu Arg Gly Ile Gly Ser Gly Met Lys Tyr
                725                 730                 735

Leu Ser Asp Met Ser Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile
            740                 745                 750

Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Met Ser
        755                 760                 765

Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly
    770                 775                 780

Lys Ile Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Tyr Arg Lys
785                 790                 795                 800

Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu
                805                 810                 815

Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp
            820                 825                 830

Val Ile Lys Ala Ile Glu Glu Gly Tyr Arg Leu Pro Pro Pro Met Asp
        835                 840                 845

Cys Pro Ile Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Glu
    850                 855                 860

Arg Ser Asp Arg Pro Lys Phe Gly Gln Ile Val Asn Met Leu Asp Lys
865                 870                 875                 880

Leu Ile Arg Asn Pro Asn Ser Leu Lys Arg Thr Gly Thr Glu Ser Ser
                885                 890                 895

Arg Pro Asn Thr Ala Leu Leu Asp Pro Ser Ser Pro Glu Phe Ser Ala
            900                 905                 910

Val Val Ser Val Gly Asp Trp Leu Gln Ala Ile Lys Met Asp Arg Tyr
        915                 920                 925

Lys Asp Asn Phe Thr Ala Ala Gly Tyr Thr Thr Leu Glu Ala Val Val
    930                 935                 940

His Val Asn Gln Glu Asp Leu Ala Arg Ile Gly Ile Thr Ala Ile Thr
945                 950                 955                 960

His Gln Asn Lys Ile Leu Ser Ser Val Gln Ala Met Arg Thr Gln Met
                965                 970                 975

Gln Gln Met His Gly Arg Met Val Pro Val
            980                 985
```

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4529 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 186..3182

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
CGGTGCGAGC GAACAGGAGT GGGGGGGAAA TTAAAAAAAG CTAAACGTGG AGCAGCCGAT      60

CGGGGACCGA GAAGGGGAAT CGATGCAAGG AGCACACTAA AACAAAAGCT ACTTCGGAAC     120

AAACAGCATT TAAAAATCCA CGACTCAAGA TAACTGAAAC CTAAAATAAA ACCTGCTCAT     180

GCACC ATG GTT TTT CAA ACT CGG TAC CCT TCA TGG ATT ATT TTA TGC          227
      Met Val Phe Gln Thr Arg Tyr Pro Ser Trp Ile Ile Leu Cys
        1               5                  10

TAC ATC TGG CTG CTC CGC TTT GCA CAC ACA GGG GAG GCG CAG GCT GCG       275
Tyr Ile Trp Leu Leu Arg Phe Ala His Thr Gly Glu Ala Gln Ala Ala
 15                  20                  25                  30

AAG GAA GTA CTA CTG CTG GAT TCT AAA GCA CAA CAA ACA GAG TTG GAG       323
Lys Glu Val Leu Leu Leu Asp Ser Lys Ala Gln Gln Thr Glu Leu Glu
                35                  40                  45

TGG ATT TCC TCT CCA CCC AAT GGG TGG GAA GAA ATT AGT GGT TTG GAT       371
Trp Ile Ser Ser Pro Pro Asn Gly Trp Glu Glu Ile Ser Gly Leu Asp
            50                  55                  60

GAG AAC TAT ACC CCG ATA CGA ACA TAC CAG GTG TGC CAA GTC ATG GAG       419
Glu Asn Tyr Thr Pro Ile Arg Thr Tyr Gln Val Cys Gln Val Met Glu
        65                  70                  75

CCC AAC CAA AAC AAC TGG CTG CGG ACT AAC TGG ATT TCC AAA GGC AAT       467
Pro Asn Gln Asn Asn Trp Leu Arg Thr Asn Trp Ile Ser Lys Gly Asn
     80                  85                  90

GCA CAA AGG ATT TTT GTA GAA TTG AAA TTC ACC CTG AGG GAT TGT AAC       515
Ala Gln Arg Ile Phe Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn
 95                  100                 105                 110

AGT CTT CCT GGA GTA CTG GGA ACT TGC AAG GAA ACA TTT AAT TTG TAC       563
Ser Leu Pro Gly Val Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr
                115                 120                 125
```

```
TAT TAT GAA ACA GAC TAT GAC ACT GGC AGG AAT ATA AGA GAA AAC CTC        611
Tyr Tyr Glu Thr Asp Tyr Asp Thr Gly Arg Asn Ile Arg Glu Asn Leu
            130                 135                 140

TAT GTA AAA ATA GAC ACC ATT GCT GCA GAT GAA AGT TTT ACC CAA GGT        659
Tyr Val Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Gly
        145                 150                 155

GAC CTT GGT GAA AGA AAG ATG AAG CTT AAC ACT GAG GTG AGA GAG ATT        707
Asp Leu Gly Glu Arg Lys Met Lys Leu Asn Thr Glu Val Arg Glu Ile
    160                 165                 170

GGA CCT TTG TCC AAA AAG GGA TTC TAT CTT GCC TTT CAG GAT GTA GGG        755
Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly
175                 180                 185                 190

GCT TGC ATA GCT TTG GTT TCT GTC AAA GTG TAC TAC AAG AAG TGC TGG        803
Ala Cys Ile Ala Leu Val Ser Val Lys Val Tyr Tyr Lys Lys Cys Trp
                195                 200                 205

TCC ATT ATT GAG AAC TTA GCT ATC TTT CCA GAT ACA GTG ACT GGT TCA        851
Ser Ile Ile Glu Asn Leu Ala Ile Phe Pro Asp Thr Val Thr Gly Ser
            210                 215                 220

GAA TTT TCC TCT TTA GTC GAG GTT CGA GGG ACA TGT GTC AGC AGT GCA        899
Glu Phe Ser Ser Leu Val Glu Val Arg Gly Thr Cys Val Ser Ser Ala
        225                 230                 235

GAG GAA GAA GCG GAA AAC GCC CCC AGG ATG CAC TGC AGT GCA GAA GGA        947
Glu Glu Glu Ala Glu Asn Ala Pro Arg Met His Cys Ser Ala Glu Gly
    240                 245                 250

GAA TGG TTA GTG CCC ATT GGA AAA TGT ATC TGC AAA GCA GGC TAC CAG        995
Glu Trp Leu Val Pro Ile Gly Lys Cys Ile Cys Lys Ala Gly Tyr Gln
255                 260                 265                 270

CAA AAA GGA GAC ACT TGT GAA CCC TGT GGC CGT GGG TTC TAC AAG TCT       1043
Gln Lys Gly Asp Thr Cys Glu Pro Cys Gly Arg Gly Phe Tyr Lys Ser
                275                 280                 285

TCC TCT CAA GAT CTT CAG TGC TCT CGT TGT CCA ACT CAC AGT TTT TCT       1091
Ser Ser Gln Asp Leu Gln Cys Ser Arg Cys Pro Thr His Ser Phe Ser
            290                 295                 300

GAT AAA GAA GGC TCC TCC AGA TGT GAA TGT GAA GAT GGG TAT TAC AGG       1139
Asp Lys Glu Gly Ser Ser Arg Cys Glu Cys Glu Asp Gly Tyr Tyr Arg
        305                 310                 315

GCT CCA TCT GAC CCA CCA TAC GTT GCA TGC ACA AGG CCT CCA TCT GCA       1187
Ala Pro Ser Asp Pro Pro Tyr Val Ala Cys Thr Arg Pro Pro Ser Ala
    320                 325                 330

CCA CAG AAC CTC ATT TTC AAC ATC AAC CAA ACC ACA GTA AGT TTG GAA       1235
Pro Gln Asn Leu Ile Phe Asn Ile Asn Gln Thr Thr Val Ser Leu Glu
335                 340                 345                 350
```

```
TGG AGT CCT CCT GCA GAC AAT GGG GGA AGA AAC GAT GTG ACC TAC AGA      1283
Trp Ser Pro Pro Ala Asp Asn Gly Gly Arg Asn Asp Val Thr Tyr Arg
                355                 360                 365

ATA TTG TGT AAG CGG TGC AGT TGG GAG CAG GGC GAA TGT GTT CCC TGT      1331
Ile Leu Cys Lys Arg Cys Ser Trp Glu Gln Gly Glu Cys Val Pro Cys
            370                 375                 380

GGG AGT AAC ATT GGA TAC ATG CCC CAG CAG ACT GGA TTA GAG GAT AAC      1379
Gly Ser Asn Ile Gly Tyr Met Pro Gln Gln Thr Gly Leu Glu Asp Asn
        385                 390                 395

TAT GTC ACT GTC ATG GAC CTG CTA GCC CAC GCT AAT TAT ACT TTT GAA      1427
Tyr Val Thr Val Met Asp Leu Leu Ala His Ala Asn Tyr Thr Phe Glu
    400                 405                 410

GTT GAA GCT GTA AAT GGA GTT TCT GAC TTA AGC CGA TCC CAG AGG CTC      1475
Val Glu Ala Val Asn Gly Val Ser Asp Leu Ser Arg Ser Gln Arg Leu
415                 420                 425                 430

TTT GCT GCT GTC AGT ATC ACC ACT GGT CAA GCA GCT CCC TCG CAA GTG      1523
Phe Ala Ala Val Ser Ile Thr Thr Gly Gln Ala Ala Pro Ser Gln Val
                435                 440                 445

AGC GGA GTA ATG AAG GAG AGA GTA CTG CAG CGG AGT GTC GAG CTT TCC      1571
Ser Gly Val Met Lys Glu Arg Val Leu Gln Arg Ser Val Glu Leu Ser
            450                 455                 460

TGG CAG GAA CCA GAG CAT CCC AAT GGA GTC ATC ACA GAA TAT GAA ATC      1619
Trp Gln Glu Pro Glu His Pro Asn Gly Val Ile Thr Glu Tyr Glu Ile
        465                 470                 475

AAG TAT TAC GAG AAA GAT CAA AGG GAA CGG ACC TAC TCA ACA GTA AAA      1667
Lys Tyr Tyr Glu Lys Asp Gln Arg Glu Arg Thr Tyr Ser Thr Val Lys
    480                 485                 490

ACC AAG TCT ACT TCA GCC TCC ATT AAT AAT CTG AAA CCA GGA ACA GTG      1715
Thr Lys Ser Thr Ser Ala Ser Ile Asn Asn Leu Lys Pro Gly Thr Val
495                 500                 505                 510

TAT GTT TTC CAG ATT CGG GCT TTT ACT GCT GCT GGT TAT GGA AAT TAC      1763
Tyr Val Phe Gln Ile Arg Ala Phe Thr Ala Ala Gly Tyr Gly Asn Tyr
                515                 520                 525

AGT CCC AGA CTT GAT GTT GCT ACA CTA GAG GAA GCT ACA GGT AAA ATG      1811
Ser Pro Arg Leu Asp Val Ala Thr Leu Glu Glu Ala Thr Gly Lys Met
            530                 535                 540

TTT GAA GCT ACA GCT GTC TCC AGT GAA CAG AAT CCT GTT ATT ATC ATT      1859
Phe Glu Ala Thr Ala Val Ser Ser Glu Gln Asn Pro Val Ile Ile Ile
        545                 550                 555

GCT GTG GTT GCT GTA GCT GGG ACC ATC ATT TTG GTG TTC ATG GTC TTT      1907
Ala Val Val Ala Val Ala Gly Thr Ile Ile Leu Val Phe Met Val Phe
    560                 565                 570
```

```
GGC TTC ATC ATT GGG AGA AGG CAC TGT GGT TAT AGC AAA GCT GAC CAA      1955
Gly Phe Ile Ile Gly Arg Arg His Cys Gly Tyr Ser Lys Ala Asp Gln
575                 580                 585                 590

GAA GGC GAT GAA GAG CTT TAC TTT CAT TTT AAA TTT CCA GGC ACC AAA      2003
Glu Gly Asp Glu Glu Leu Tyr Phe His Phe Lys Phe Pro Gly Thr Lys
                595                 600                 605

ACC TAC ATT GAC CCT GAA ACC TAT GAG GAC CCA AAT AGA GCT GTC CAT      2051
Thr Tyr Ile Asp Pro Glu Thr Tyr Glu Asp Pro Asn Arg Ala Val His
            610                 615                 620

CAA TTC GCC AAG GAG CTA GAT GCC TCC TGT ATT AAA ATT GAG CGT GTG      2099
Gln Phe Ala Lys Glu Leu Asp Ala Ser Cys Ile Lys Ile Glu Arg Val
        625                 630                 635

ATT GGT GCA GGA GAA TTC GGT GAA GTC TGC AGT GGC CGT TTG AAA CTT      2147
Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Leu
    640                 645                 650

CCA GGG AAA AGA GAT GTT GCA GTA GCC ATA AAA ACC CTG AAA GTT GGT      2195
Pro Gly Lys Arg Asp Val Ala Val Ala Ile Lys Thr Leu Lys Val Gly
655                 660                 665                 670

TAC ACA GAA AAA CAA AGG AGA GAC TTT TTG TGT GAA GCA AGC ATC ATG      2243
Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Cys Glu Ala Ser Ile Met
                675                 680                 685

GGG CAG TTT GAC CAC CCA AAT GTT GTC CAT TTG GAA GGG GTT GTT ACA      2291
Gly Gln Phe Asp His Pro Asn Val Val His Leu Glu Gly Val Val Thr
            690                 695                 700

AGA GGG AAA CCA GTC ATG ATA GTA ATA GAG TTC ATG GAA AAT GGA GCC      2339
Arg Gly Lys Pro Val Met Ile Val Ile Glu Phe Met Glu Asn Gly Ala
        705                 710                 715

CTA GAT GCA TTT CTC AGG AAA CAT GAT GGG CAA TTT ACA GTC ATT CAG      2387
Leu Asp Ala Phe Leu Arg Lys His Asp Gly Gln Phe Thr Val Ile Gln
    720                 725                 730

TTA GTA GGA ATG CTG AGA GGA ATT GCT GCT GGA ATG AGA TAT TTG GCT      2435
Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Arg Tyr Leu Ala
735                 740                 745                 750

GAT ATG GGA TAT GTT CAC AGG GAC CTT GCA GCT CGC AAT ATT CTT GTC      2483
Asp Met Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val
                755                 760                 765

AAC AGC AAT CTC GTT TGT AAA GTG TCA GAT TTT GGC CTG TCC CGA GTT      2531
Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val
            770                 775                 780

ATA GAG GAT GAT CCA GAA GCT GTC TAT ACA ACT ACT GGT GGA AAA ATT      2579
Ile Glu Asp Asp Pro Glu Ala Val Tyr Thr Thr Thr Gly Gly Lys Ile
        785                 790                 795
```

```
CCA GTA AGG TGG ACA GCA CCC GAA GCC ATC CAG TAC CGG AAA TTC ACA      2627
Pro Val Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr Arg Lys Phe Thr
    800                 805                 810

TCA GCC AGT GAT GTA TGG AGC TAT GGA ATA GTC ATG TGG GAA GTT ATG      2675
Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met
815                 820                 825                 830

TCT TAT GGA GAA AGA CCT TAT TGG GAC ATG TCA AAT CAA GAT GTT ATA      2723
Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile
                835                 840                 845

AAA GCA ATA GAA GAA GGT TAT CGT TTA CCA GCA CCC ATG GAC TGC CCA      2771
Lys Ala Ile Glu Glu Gly Tyr Arg Leu Pro Ala Pro Met Asp Cys Pro
            850                 855                 860

GCT GGC CTT CAC CAG CTA ATG TTG GAT TGT TGG CAA AAG GAG CGT GCT      2819
Ala Gly Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ala
        865                 870                 875

GAA AGG CCA AAA TTT GAA CAG ATA GTT GGA ATT CTA GAC AAA ATG ATT      2867
Glu Arg Pro Lys Phe Glu Gln Ile Val Gly Ile Leu Asp Lys Met Ile
    880                 885                 890

CGA AAC CCA AAT AGT CTG AAA ACT CCC CTG GGA ACT TGT AGT AGG CCA      2915
Arg Asn Pro Asn Ser Leu Lys Thr Pro Leu Gly Thr Cys Ser Arg Pro
895                 900                 905                 910

ATA AGC CCT CTT CTG GAT CAA AAC ACT CCT GAT TTC ACT ACC TTT TGT      2963
Ile Ser Pro Leu Leu Asp Gln Asn Thr Pro Asp Phe Thr Thr Phe Cys
                915                 920                 925

TCA GTT GGA GAA TGG CTA CAA GCT ATT AAG ATG GAA AGA TAT AAA GAT      3011
Ser Val Gly Glu Trp Leu Gln Ala Ile Lys Met Glu Arg Tyr Lys Asp
            930                 935                 940

AAT TTC ACG GCA GCT GGC TAC AAT TCC CTT GAA TCA GTA GCC AGG ATG      3059
Asn Phe Thr Ala Ala Gly Tyr Asn Ser Leu Glu Ser Val Ala Arg Met
        945                 950                 955

ACT ATT GAG GAT GTG ATG AGT TTA GGG ATC ACA CTG GTT GGT CAT CAA      3107
Thr Ile Glu Asp Val Met Ser Leu Gly Ile Thr Leu Val Gly His Gln
    960                 965                 970

AAG AAA ATC ATG AGC AGC ATT CAG ACT ATG AGA GCA CAA ATG CTA CAT      3155
Lys Lys Ile Met Ser Ser Ile Gln Thr Met Arg Ala Gln Met Leu His
975                 980                 985                 990

TTA CAT GGA ACT GGC ATT CAA GTG TGATATGCAT TTCTCCCTTT TAAGGGAGAT     3209
Leu His Gly Thr Gly Ile Gln Val
                995

TACAGACTGC AAGAGAACAG TACTGGCCTT CAGTATATGC ATAGAATGCT GCTAGAAGAC    3269

AAGTGATGTC CTGGGTCCTT CCAACAGTGA AGAGAAGATT TAAGAAGCAC CTATAGACTT    3329

GAACTCCTAA GTGCCACCAG AATATATAAA AAGGGAATTT AGGATCCACC ATCGGTGGCC    3389
```

AGGAAAATAG CAGTGACAAT AAACAAAGTA CTACCTGAAA AACATCCAAA CACCTTGAGC 3449

TCTCTAACCT CCTTTTTGTC TTATAGACTT TTTAAAATGT ACATAAAGAA TTTAAGAAAG 3509

AATATATTTG TCAAATAAAA TCATGATCTT ATTGTTAAAA TTAATGAAAT ATTTTCCTTA 3569

AATATGTGAT TTCAGACTAT TCCTTTTTAA AATCATTTGT GTTTATTCTT CATAAGGACT 3629

TTGTTTTAGA AAGCTGTTTA TAGCTTTGGA CCTTTTTAGT GTTAAATCTG TAACATTACT 3689

ACACTGGGTA CCTTTGAAAG AATCTCAAAT TTCAAAAGAA ATAGCATGAT TGAAGATACA 3749

TCTCTGTTAG AACATTGGTA TCCTTTTTGT GCCATTTTAT TCTGTTTAAT CAGTGCTGTT 3809

TTGATATTGT TTGCTAATTG GCAGGTAGTC AAGAAAATGC AAGTTGCCAA GAGCTCTGAT 3869

ATTTTTTAAA AAGAATTTTT TTGTAAAGAT CAGACAACAC ACTATCTTTT CAATGAAAAA 3929

AGCAATAATG ATCCATACAT ACTATAAGGC ACTTTTAACA GATTGTTTAT AGAGTGATTT 3989

TACTAGAAAG AATTTAATAA ACTCGAAGTT TAGGTTTATG AGTATATAAA CAAATGAGGC 4049

ACTTCATCTG AAGAATGTTG GTGAAGGCAA GTCTCTGAAA GCAGAACTAT CCAGTGTTAT 4109

CTAAAAATTA ATCTGAGCAC ATCAAGATTT TTTCATTCTC GTGACATTAG GAAATTTAGG 4169

ATAAATAGTT GACATATATT TTATATCCTC TTCTGTTGAA TGCAGTCCAA ACATGAAAGG 4229

AAATAATTGT TTTATATTAT AACTCTGAAG CATGATAAAG GGGCAGTTCA CAATTTTCAC 4289

CATTTAAACA CAAATTTGCT GCACAGAATA TCACCATTGC AGTTCAAAAC AAAACAAAAC 4349

AAAAAGTCTT TTGTTTGTGA ACACTGATGC AAGAAACTTG TTAAATGAAA GGACTCTTTA 4409

CCCTAGAAGG AAGAGGTGAA GGATCTGGCT TGTTTTTAAA GCTTTATTTA TTAAACCATA 4469

TTATTTGATT ACTGTGTTAG AATTTCATAA GCAATAATTA AATGTGTCTT TATGGAATTC 4529

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 998 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met Val Phe Gln Thr Arg Tyr Pro Ser Trp Ile Ile Leu Cys Tyr Ile
1 5 10 15

Trp Leu Leu Arg Phe Ala His Thr Gly Glu Ala Gln Ala Ala Lys Glu
20 25 30

```
Val Leu Leu Leu Asp Ser Lys Ala Gln Gln Thr Glu Leu Glu Trp Ile
         35                  40                  45

Ser Ser Pro Pro Asn Gly Trp Glu Glu Ile Ser Gly Leu Asp Glu Asn
     50                  55                  60

Tyr Thr Pro Ile Arg Thr Tyr Gln Val Cys Gln Val Met Glu Pro Asn
 65                  70                  75                  80

Gln Asn Asn Trp Leu Arg Thr Asn Trp Ile Ser Lys Gly Asn Ala Gln
                 85                  90                  95

Arg Ile Phe Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn Ser Leu
            100                 105                 110

Pro Gly Val Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Tyr
        115                 120                 125

Glu Thr Asp Tyr Asp Thr Gly Arg Asn Ile Arg Glu Asn Leu Tyr Val
    130                 135                 140

Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Gly Asp Leu
145                 150                 155                 160

Gly Glu Arg Lys Met Lys Leu Asn Thr Glu Val Arg Glu Ile Gly Pro
                165                 170                 175

Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys
            180                 185                 190

Ile Ala Leu Val Ser Val Lys Val Tyr Tyr Lys Lys Cys Trp Ser Ile
        195                 200                 205

Ile Glu Asn Leu Ala Ile Phe Pro Asp Thr Val Thr Gly Ser Glu Phe
    210                 215                 220

Ser Ser Leu Val Glu Val Arg Gly Thr Cys Val Ser Ser Ala Glu Glu
225                 230                 235                 240

Glu Ala Glu Asn Ala Pro Arg Met His Cys Ser Ala Glu Gly Glu Trp
                245                 250                 255

Leu Val Pro Ile Gly Lys Cys Ile Cys Lys Ala Gly Tyr Gln Gln Lys
            260                 265                 270

Gly Asp Thr Cys Glu Pro Cys Gly Arg Gly Phe Tyr Lys Ser Ser Ser
        275                 280                 285

Gln Asp Leu Gln Cys Ser Arg Cys Pro Thr His Ser Phe Ser Asp Lys
    290                 295                 300

Glu Gly Ser Ser Arg Cys Glu Cys Glu Asp Gly Tyr Tyr Arg Ala Pro
305                 310                 315                 320

Ser Asp Pro Pro Tyr Val Ala Cys Thr Arg Pro Pro Ser Ala Pro Gln
                325                 330                 335
```

```
Asn Leu Ile Phe Asn Ile Asn Gln Thr Thr Val Ser Leu Glu Trp Ser
            340                 345                 350

Pro Pro Ala Asp Asn Gly Gly Arg Asn Asp Val Thr Tyr Arg Ile Leu
        355                 360                 365

Cys Lys Arg Cys Ser Trp Glu Gln Gly Glu Cys Val Pro Cys Gly Ser
    370                 375                 380

Asn Ile Gly Tyr Met Pro Gln Gln Thr Gly Leu Glu Asp Asn Tyr Val
385                 390                 395                 400

Thr Val Met Asp Leu Leu Ala His Ala Asn Tyr Thr Phe Glu Val Glu
                405                 410                 415

Ala Val Asn Gly Val Ser Asp Leu Ser Arg Ser Gln Arg Leu Phe Ala
            420                 425                 430

Ala Val Ser Ile Thr Thr Gly Gln Ala Ala Pro Ser Gln Val Ser Gly
        435                 440                 445

Val Met Lys Glu Arg Val Leu Gln Arg Ser Val Glu Leu Ser Trp Gln
    450                 455                 460

Glu Pro Glu His Pro Asn Gly Val Ile Thr Glu Tyr Glu Ile Lys Tyr
465                 470                 475                 480

Tyr Glu Lys Asp Gln Arg Glu Arg Thr Tyr Ser Thr Val Lys Thr Lys
                485                 490                 495

Ser Thr Ser Ala Ser Ile Asn Asn Leu Lys Pro Gly Thr Val Tyr Val
            500                 505                 510

Phe Gln Ile Arg Ala Phe Thr Ala Ala Gly Tyr Gly Asn Tyr Ser Pro
        515                 520                 525

Arg Leu Asp Val Ala Thr Leu Glu Glu Ala Thr Gly Lys Met Phe Glu
    530                 535                 540

Ala Thr Ala Val Ser Ser Glu Gln Asn Pro Val Ile Ile Ile Ala Val
545                 550                 555                 560

Val Ala Val Ala Gly Thr Ile Ile Leu Val Phe Met Val Phe Gly Phe
                565                 570                 575

Ile Ile Gly Arg Arg His Cys Gly Tyr Ser Lys Ala Asp Gln Glu Gly
            580                 585                 590

Asp Glu Glu Leu Tyr Phe His Phe Lys Phe Pro Gly Thr Lys Thr Tyr
        595                 600                 605

Ile Asp Pro Glu Thr Tyr Glu Asp Pro Asn Arg Ala Val His Gln Phe
    610                 615                 620

Ala Lys Glu Leu Asp Ala Ser Cys Ile Lys Ile Glu Arg Val Ile Gly
625                 630                 635                 640
```

```
Ala Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Leu Pro Gly
                645                 650                 655

Lys Arg Asp Val Ala Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr
            660                 665                 670

Glu Lys Gln Arg Arg Asp Phe Leu Cys Glu Ala Ser Ile Met Gly Gln
        675                 680                 685

Phe Asp His Pro Asn Val Val His Leu Glu Gly Val Val Thr Arg Gly
    690                 695                 700

Lys Pro Val Met Ile Val Ile Glu Phe Met Glu Asn Gly Ala Leu Asp
705                 710                 715                 720

Ala Phe Leu Arg Lys His Asp Gly Gln Phe Thr Val Ile Gln Leu Val
                725                 730                 735

Gly Met Leu Arg Gly Ile Ala Ala Gly Met Arg Tyr Leu Ala Asp Met
            740                 745                 750

Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser
        755                 760                 765

Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Ile Glu
    770                 775                 780

Asp Asp Pro Glu Ala Val Tyr Thr Thr Thr Gly Gly Lys Ile Pro Val
785                 790                 795                 800

Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr Arg Lys Phe Thr Ser Ala
                805                 810                 815

Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met Ser Tyr
            820                 825                 830

Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile Lys Ala
        835                 840                 845

Ile Glu Glu Gly Tyr Arg Leu Pro Ala Pro Met Asp Cys Pro Ala Gly
    850                 855                 860

Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ala Glu Arg
865                 870                 875                 880

Pro Lys Phe Glu Gln Ile Val Gly Ile Leu Asp Lys Met Ile Arg Asn
                885                 890                 895

Pro Asn Ser Leu Lys Thr Pro Leu Gly Thr Cys Ser Arg Pro Ile Ser
            900                 905                 910

Pro Leu Leu Asp Gln Asn Thr Pro Asp Phe Thr Thr Phe Cys Ser Val
        915                 920                 925

Gly Glu Trp Leu Gln Ala Ile Lys Met Glu Arg Tyr Lys Asp Asn Phe
    930                 935                 940
```

```
Thr Ala Ala Gly Tyr Asn Ser Leu Glu Ser Val Ala Arg Met Thr Ile
945                 950                 955                 960

Glu Asp Val Met Ser Leu Gly Ile Thr Leu Val Gly His Gln Lys Lys
                965                 970                 975

Ile Met Ser Ser Ile Gln Thr Met Arg Ala Gln Met Leu His Leu His
            980                 985                 990

Gly Thr Gly Ile Gln Val
        995
```

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 976 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

```
Met Glu Leu Gln Ala Ala Arg Ala Cys Phe Ala Leu Leu Trp Gly Cys
1               5                   10                  15

Ala Leu Ala Ala Ala Ala Ala Ala Gln Gly Lys Glu Val Val Leu Leu
            20                  25                  30

Asp Phe Ala Ala Ala Gly Gly Glu Leu Gly Trp Leu Thr His Pro Tyr
        35                  40                  45

Gly Lys Gly Trp Asp Leu Met Gln Asn Ile Met Asn Asp Met Pro Ile
    50                  55                  60

Tyr Met Tyr Ser Val Cys Asn Val Met Ser Gly Asp Gln Asp Asn Trp
65                  70                  75                  80

Leu Arg Thr Asn Trp Val Tyr Arg Gly Glu Ala Glu Arg Asn Asn Phe
                85                  90                  95

Glu Leu Asn Phe Thr Val Arg Asp Cys Asn Ser Phe Pro Gly Gly Ala
            100                 105                 110

Ser Ser Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Ala Glu Ser Asp Leu
        115                 120                 125

Asp Tyr Gly Thr Asn Phe Gln Lys Arg Leu Phe Thr Lys Ile Asp Thr
    130                 135                 140

Ile Ala Pro Asp Glu Ile Thr Val Ser Ser Asp Phe Glu Ala Arg His
145                 150                 155                 160
```

Val Lys Leu Asn Val Glu Glu Arg Ser Val Gly Pro Leu Thr Arg Lys
165 170 175

Gly Phe Tyr Leu Ala Phe Gln Asp Ile Gly Ala Cys Val Ala Leu Leu
180 185 190

Ser Val Arg Val Tyr Tyr Lys Lys Cys Pro Glu Leu Leu Gln Gly Leu
195 200 205

Ala His Phe Pro Glu Thr Ile Ala Gly Ser Asp Ala Pro Ser Leu Ala
210 215 220

Thr Val Ala Gly Thr Cys Val Asp His Ala Val Val Pro Pro Gly Gly
225 230 235 240

Glu Glu Pro Arg Met His Cys Ala Val Asp Gly Glu Trp Leu Val Pro
245 250 255

Ile Gly Gln Cys Leu Cys Gln Ala Gly Tyr Glu Lys Val Glu Asp Ala
260 265 270

Cys Gln Ala Cys Ser Pro Gly Phe Phe Lys Phe Glu Ala Ser Glu Ser
275 280 285

Pro Cys Leu Glu Cys Pro Glu His Thr Leu Pro Ser Pro Glu Gly Ala
290 295 300

Thr Ser Cys Glu Cys Glu Glu Gly Phe Phe Arg Ala Pro Gln Asp Pro
305 310 315 320

Ala Ser Met Pro Cys Thr Arg Pro Pro Ser Ala Pro His Tyr Leu Thr
325 330 335

Ala Val Gly Met Gly Ala Lys Val Glu Leu Arg Trp Thr Pro Pro Gln
340 345 350

Asp Ser Gly Gly Arg Glu Asp Ile Val Tyr Ser Val Thr Cys Glu Gln
355 360 365

Cys Trp Pro Glu Ser Gly Glu Cys Gly Pro Cys Glu Ala Ser Val Arg
370 375 380

Tyr Ser Glu Pro Pro His Gly Leu Thr Arg Thr Ser Val Thr Val Ser
385 390 395 400

Asp Leu Glu Pro His Met Asn Tyr Thr Phe Thr Val Glu Ala Arg Asn
405 410 415

Gly Val Ser Gly Leu Val Thr Ser Arg Ser Phe Arg Thr Ala Ser Val
420 425 430

Ser Ile Asn Gln Thr Glu Pro Pro Lys Val Arg Leu Glu Gly Arg Ser
435 440 445

Thr Thr Ser Leu Ser Val Ser Trp Ser Ile Pro Pro Pro Gln Gln Ser
450 455 460

```
Arg Val Trp Lys Tyr Glu Val Thr Tyr Arg Lys Lys Gly Asp Ser Asn
465                 470                 475                 480

Ser Tyr Asn Val Arg Arg Thr Glu Gly Phe Ser Val Thr Leu Asp Asp
                485                 490                 495

Leu Ala Pro Asp Thr Thr Tyr Leu Val Gln Val Gln Ala Leu Thr Gln
            500                 505                 510

Glu Gly Gln Gly Ala Gly Ser Lys Val His Glu Phe Gln Thr Leu Ser
        515                 520                 525

Pro Glu Gly Ser Gly Asn Leu Ala Val Ile Gly Gly Val Ala Val Gly
    530                 535                 540

Val Val Leu Leu Leu Val Leu Ala Gly Val Gly Phe Phe Ile His Arg
545                 550                 555                 560

Arg Arg Lys Asn Gln Arg Ala Arg Gln Ser Pro Glu Asp Val Tyr Phe
                565                 570                 575

Ser Lys Ser Glu Gln Leu Lys Pro Leu Lys Thr Tyr Val Asp Pro His
            580                 585                 590

Thr Tyr Glu Asp Pro Asn Gln Ala Val Leu Lys Phe Thr Thr Glu Ile
        595                 600                 605

His Pro Ser Cys Val Thr Arg Gln Lys Val Ile Gly Ala Gly Glu Phe
    610                 615                 620

Gly Glu Val Tyr Lys Gly Met Leu Lys Thr Ser Ser Gly Lys Lys Glu
625                 630                 635                 640

Val Pro Val Ala Ile Lys Thr Leu Lys Ala Gly Tyr Thr Glu Lys Gln
                645                 650                 655

Arg Val Asp Phe Leu Gly Glu Ala Gly Ile Met Gly Gln Phe Ser His
            660                 665                 670

His Asn Ile Ile Arg Leu Glu Gly Val Ile Ser Lys Tyr Lys Pro Met
        675                 680                 685

Met Ile Ile Thr Glu Tyr Met Glu Asn Gly Ala Leu Asp Lys Phe Leu
    690                 695                 700

Arg Glu Lys Asp Gly Glu Phe Ser Val Leu Gln Leu Val Gly Met Leu
705                 710                 715                 720

Arg Gly Ile Ala Ala Gly Met Lys Tyr Leu Ala Asn Met Asn Tyr Val
                725                 730                 735

His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val
            740                 745                 750

Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp Pro
        755                 760                 765
```

```
Glu Ala Thr Tyr Thr Thr Ser Gly Gly Lys Ile Pro Ile Arg Trp Thr
    770                 775                 780

Ala Pro Glu Ala Ile Ser Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val
785                 790                 795                 800

Trp Ser Phe Gly Ile Val Met Trp Glu Val Met Thr Tyr Gly Glu Arg
                805                 810                 815

Pro Tyr Trp Glu Leu Ser Asn His Glu Val Met Lys Ala Ile Asn Asp
            820                 825                 830

Gly Phe Arg Leu Pro Thr Pro Met Asp Cys Pro Ser Ala Ile Tyr Gln
        835                 840                 845

Leu Met Met Gln Cys Trp Gln Gln Glu Arg Ala Arg Arg Pro Lys Phe
    850                 855                 860

Ala Asp Ile Val Ser Ile Leu Asp Lys Leu Ile Arg Ala Pro Asp Ser
865                 870                 875                 880

Leu Lys Thr Leu Ala Asp Phe Asp Pro Arg Val Ser Ile Arg Leu Pro
                885                 890                 895

Ser Thr Ser Gly Ser Glu Gly Val Pro Phe Arg Thr Val Ser Glu Trp
            900                 905                 910

Leu Glu Ser Ile Lys Met Gln Gln Tyr Thr Glu His Phe Met Ala Ala
        915                 920                 925

Gly Tyr Thr Ala Ile Glu Lys Val Val Gln Met Thr Asn Asp Asp Ile
    930                 935                 940

Lys Arg Ile Gly Val Arg Leu Pro Gly His Gln Lys Arg Ile Ala Tyr
945                 950                 955                 960

Ser Leu Leu Gly Leu Lys Asp Gln Val Asn Thr Val Gly Ile Pro Ile
                965                 970                 975
```

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 984 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

```
Met Glu Arg Arg Trp Pro Leu Gly Leu Gly Leu Val Leu Leu Leu Cys
1               5                   10                  15
```

```
Ala Pro Leu Pro Pro Gly Ala Arg Ala Lys Glu Val Thr Leu Met Asp
            20                  25                  30

Thr Ser Lys Ala Gln Gly Glu Leu Gly Trp Leu Leu Asp Pro Pro Lys
        35                  40                  45

Asp Gly Trp Ser Glu Gln Gln Gln Ile Leu Asn Gly Thr Pro Leu Tyr
    50                  55                  60

Met Tyr Gln Asp Cys Pro Met Gln Gly Arg Arg Asp Thr Asp His Trp
65                  70                  75                  80

Leu Arg Ser Asn Trp Ile Tyr Arg Gly Glu Glu Ala Ser Arg Val His
                85                  90                  95

Val Glu Leu Gln Phe Thr Val Arg Asp Cys Lys Ser Phe Pro Gly Gly
            100                 105                 110

Ala Gly Pro Leu Gly Cys Lys Glu Thr Phe Asn Leu Leu Tyr Met Glu
        115                 120                 125

Ser Asp Gln Asp Val Gly Ile Gln Leu Arg Arg Pro Leu Phe Gln Lys
    130                 135                 140

Val Thr Thr Val Ala Ala Asp Gln Ser Phe Thr Ile Arg Asp Leu Ala
145                 150                 155                 160

Ser Gly Ser Val Lys Leu Asn Val Glu Arg Cys Ser Leu Gly Arg Leu
                165                 170                 175

Thr Arg Arg Gly Leu Tyr Leu Ala Phe His Asn Pro Gly Ala Cys Val
            180                 185                 190

Ala Leu Val Ser Val Arg Val Phe Tyr Gln Arg Cys Pro Glu Thr Leu
        195                 200                 205

Asn Gly Leu Ala Gln Phe Pro Asp Thr Leu Pro Gly Pro Ala Gly Leu
    210                 215                 220

Val Glu Val Ala Gly Thr Cys Leu Pro His Ala Arg Ala Ser Pro Arg
225                 230                 235                 240

Pro Ser Gly Ala Pro Arg Met His Cys Ser Pro Asp Gly Glu Trp Leu
                245                 250                 255

Val Pro Val Gly Arg Cys His Cys Glu Pro Gly Tyr Glu Glu Gly Gly
            260                 265                 270

Ser Gly Glu Ala Cys Val Ala Cys Pro Ser Gly Ser Tyr Arg Met Asp
        275                 280                 285

Met Asp Thr Pro His Cys Leu Thr Cys Pro Gln Gln Ser Thr Ala Glu
    290                 295                 300

Ser Glu Gly Ala Thr Ile Cys Thr Cys Glu Ser Gly His Tyr Arg Ala
305                 310                 315                 320
```

Pro Gly Glu Gly Pro Gln Val Ala Cys Thr Gly Pro Pro Ser Ala Pro
325 330 335

Arg Asn Leu Ser Phe Ser Ala Ser Gly Thr Gln Leu Ser Leu Arg Trp
340 345 350

Glu Pro Pro Ala Asp Thr Gly Gly Arg Gln Asp Val Arg Tyr Ser Val
355 360 365

Arg Cys Ser Gln Cys Gln Gly Thr Ala Gln Asp Gly Gly Pro Cys Gln
370 375 380

Pro Cys Gly Val Gly Val His Phe Ser Pro Gly Ala Arg Ala Leu Thr
385 390 395 400

Thr Pro Ala Val His Val Asn Gly Leu Glu Pro Tyr Ala Asn Tyr Thr
405 410 415

Phe Asn Val Glu Ala Gln Asn Gly Val Ser Gly Leu Gly Ser Ser Gly
420 425 430

His Ala Ser Thr Ser Val Ser Ile Ser Met Gly His Ala Glu Ser Leu
435 440 445

Ser Gly Leu Ser Leu Arg Leu Val Lys Lys Glu Pro Arg Gln Leu Glu
450 455 460

Leu Thr Trp Ala Gly Ser Arg Pro Arg Ser Pro Gly Ala Asn Leu Thr
465 470 475 480

Tyr Glu Leu His Val Leu Asn Gln Asp Glu Glu Arg Tyr Gln Met Val
485 490 495

Leu Glu Pro Arg Val Leu Leu Thr Glu Leu Gln Pro Asp Thr Thr Tyr
500 505 510

Ile Val Arg Val Arg Met Leu Thr Pro Leu Gly Pro Gly Pro Phe Ser
515 520 525

Pro Asp His Glu Phe Arg Thr Ser Pro Pro Val Ser Arg Gly Leu Thr
530 535 540

Gly Gly Glu Ile Val Ala Val Ile Phe Gly Leu Leu Leu Gly Ala Ala
545 550 555 560

Leu Leu Leu Gly Ile Leu Val Phe Arg Ser Arg Arg Ala Gln Arg Gln
565 570 575

Arg Gln Gln Arg His Val Thr Ala Pro Pro Met Trp Ile Glu Arg Thr
580 585 590

Ser Cys Ala Glu Ala Leu Cys Gly Thr Ser Arg His Thr Arg Thr Leu
595 600 605

His Arg Glu Pro Trp Thr Leu Pro Gly Gly Trp Ser Asn Phe Pro Ser
610 615 620

```
Arg Glu Leu Asp Pro Ala Trp Leu Met Val Asp Thr Val Ile Gly Glu
625                 630                 635                 640

Gly Glu Phe Gly Glu Val Tyr Arg Gly Thr Leu Arg Leu Pro Ser Gln
                645                 650                 655

Asp Cys Lys Thr Val Ala Ile Lys Thr Leu Lys Asp Thr Ser Pro Gly
            660                 665                 670

Gly Gln Trp Trp Asn Phe Leu Arg Glu Ala Thr Ile Met Gly Gln Phe
        675                 680                 685

Ser His Pro His Ile Leu His Leu Glu Gly Val Val Thr Lys Arg Lys
    690                 695                 700

Pro Ile Met Ile Ile Thr Glu Phe Met Glu Asn Ala Ala Leu Asp Ala
705                 710                 715                 720

Phe Leu Arg Glu Arg Glu Asp Gln Leu Val Pro Gly Gln Leu Val Ala
                725                 730                 735

Met Leu Gln Gly Ile Ala Ser Gly Met Asn Tyr Leu Ser Asn His Asn
            740                 745                 750

Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Gln Asn
        755                 760                 765

Leu Cys Cys Lys Val Ser Asp Phe Gly Leu Thr Arg Leu Leu Asp Asp
    770                 775                 780

Phe Asp Gly Thr Tyr Glu Thr Gln Gly Gly Lys Ile Pro Ile Arg Trp
785                 790                 795                 800

Thr Ala Pro Glu Ala Ile Ala His Arg Ile Phe Thr Thr Ala Ser Asp
                805                 810                 815

Val Trp Ser Phe Gly Ile Val Met Trp Glu Val Leu Ser Phe Gly Asp
            820                 825                 830

Lys Pro Tyr Gly Glu Met Ser Asn Gln Glu Val Met Lys Ser Ile Glu
        835                 840                 845

Asp Gly Tyr Arg Leu Pro Pro Pro Val Asp Cys Pro Ala Pro Leu Tyr
    850                 855                 860

Glu Leu Met Lys Asn Cys Trp Ala Tyr Asp Arg Ala Arg Arg Pro His
865                 870                 875                 880

Phe Gln Lys Leu Gln Ala His Leu Glu Gln Leu Leu Ala Asn Pro His
                885                 890                 895

Ser Leu Arg Thr Ile Ala Asn Phe Asp Pro Arg Val Thr Leu Arg Leu
            900                 905                 910

Pro Ser Leu Ser Gly Ser Asp Gly Ile Pro Tyr Arg Thr Val Ser Glu
        915                 920                 925
```

```
Trp Leu Glu Ser Ile Arg Met Lys Arg Tyr Ile Leu His Phe His Ser
    930                 935                 940

Ala Gly Leu Asp Thr Met Glu Cys Val Leu Glu Leu Thr Ala Glu Asp
945                 950                 955                 960

Leu Thr Gln Met Gly Ile Thr Leu Pro Gly His Gln Lys Arg Ile Leu
                965                 970                 975

Cys Ser Ile Gln Gly Phe Lys Asp
            980
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 998 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

```
Met Ala Arg Ala Arg Pro Pro Pro Pro Pro Ser Pro Pro Pro Gly Leu
1               5                   10                  15

Leu Pro Leu Leu Pro Pro Leu Leu Leu Leu Pro Leu Leu Leu Leu Pro
            20                  25                  30

Ala Gly Cys Arg Ala Leu Glu Glu Thr Leu Met Asp Thr Lys Trp Val
        35                  40                  45

Thr Ser Glu Leu Ala Trp Thr Ser His Pro Glu Ser Gly Trp Glu Glu
    50                  55                  60

Val Ser Gly Tyr Asp Glu Ala Met Asn Pro Ile Arg Thr Tyr Gln Val
65                  70                  75                  80

Cys Asn Val Arg Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr Gly Phe
                85                  90                  95

Ile Trp Arg Arg Asp Val Gln Arg Val Tyr Val Glu Leu Lys Phe Thr
            100                 105                 110

Val Arg Asp Cys Asn Ser Ile Pro Asn Ile Pro Gly Ser Cys Lys Glu
        115                 120                 125

Thr Phe Asn Leu Phe Tyr Tyr Glu Ala Asp Ser Asp Val Ala Ser Ala
    130                 135                 140

Ser Ser Pro Phe Trp Met Glu Asn Pro Tyr Val Lys Val Asp Thr Ile
145                 150                 155                 160

Ala Pro Asp Glu Ser Phe Ser Arg Leu Asp Ala Gly Arg Val Asn Thr
                165                 170                 175
```

```
Lys Val Arg Ser Phe Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu Ala
            180                 185                 190

Phe Gln Asp Gln Gly Ala Cys Met Ser Leu Ile Ser Val Arg Ala Phe
        195                 200                 205

Tyr Lys Lys Cys Ala Ser Thr Thr Ala Gly Phe Ala Leu Phe Pro Glu
    210                 215                 220

Thr Leu Thr Gly Ala Glu Pro Thr Ser Leu Val Ile Ala Pro Gly Thr
225                 230                 235                 240

Cys Ile Pro Asn Ala Val Glu Val Ser Val Pro Leu Lys Leu Tyr Cys
                245                 250                 255

Asn Gly Asp Gly Glu Trp Met Val Pro Val Gly Ala Cys Thr Cys Ala
            260                 265                 270

Thr Gly His Glu Pro Ala Ala Lys Glu Ser Gln Cys Arg Pro Cys Pro
        275                 280                 285

Pro Gly Ser Tyr Lys Ala Lys Gln Gly Glu Gly Pro Cys Leu Pro Cys
    290                 295                 300

Pro Pro Asn Ser Arg Thr Thr Ser Pro Ala Ala Ser Ile Cys Thr Cys
305                 310                 315                 320

His Asn Asn Phe Tyr Arg Ala Asp Ser Asp Ser Ala Asp Ser Ala Cys
                325                 330                 335

Thr Thr Val Pro Ser Pro Pro Arg Gly Val Ile Ser Asn Val Asn Glu
            340                 345                 350

Thr Ser Leu Ile Leu Glu Trp Ser Glu Pro Arg Asp Leu Gly Val Arg
        355                 360                 365

Asp Asp Leu Leu Tyr Asn Val Ile Cys Lys Lys Cys His Gly Ala Gly
    370                 375                 380

Gly Ala Ser Ala Cys Ser Arg Cys Asp Asp Asn Val Glu Phe Val Pro
385                 390                 395                 400

Arg Gln Leu Gly Leu Ser Glu Pro Arg Val His Thr Ser His Leu Leu
                405                 410                 415

Ala His Thr Arg Tyr Thr Phe Glu Val Gln Ala Val Asn Gly Val Ser
            420                 425                 430

Gly Lys Ser Pro Leu Pro Pro Arg Tyr Ala Ala Val Asn Ile Thr Thr
        435                 440                 445

Asn Gln Ala Ala Pro Ser Glu Val Pro Thr Leu Arg Leu His Ser Ser
    450                 455                 460

Ser Gly Ser Ser Leu Thr Leu Ser Trp Ala Pro Pro Glu Arg Pro Asn
465                 470                 475                 480
```

Gly Val Ile Leu Asp Tyr Glu Met Lys Tyr Phe Glu Lys Ser Glu Gly
485 490 495

Ile Ala Ser Thr Val Thr Ser Gln Met Asn Ser Val Gln Leu Asp Gly
500 505 510

Leu Arg Pro Asp Ala Arg Tyr Val Val Gln Val Arg Ala Arg Thr Val
515 520 525

Ala Gly Tyr Gly Gln Tyr Ser Arg Pro Ala Glu Phe Glu Thr Thr Ser
530 535 540

Glu Arg Gly Ser Gly Ala Gln Gln Leu Gln Glu Gln Leu Pro Leu Ile
545 550 555 560

Val Gly Ser Ala Thr Ala Gly Leu Val Phe Val Val Ala Val Val Val
565 570 575

Ile Ala Ile Val Cys Leu Arg Lys Gln Arg His Gly Ser Asp Ser Glu
580 585 590

Tyr Thr Glu Lys Leu Gln Gln Tyr Ile Ala Pro Gly Met Lys Val Tyr
595 600 605

Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala Val Arg Glu Phe
610 615 620

Ala Lys Glu Ile Asp Val Ser Cys Val Lys Ile Glu Glu Val Ile Gly
625 630 635 640

Ala Gly Glu Phe Gly Glu Val Cys Arg Gly Arg Leu Lys Gln Pro Gly
645 650 655

Arg Arg Glu Val Phe Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr
660 665 670

Glu Arg Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met Gly Gln
675 680 685

Phe Asp His Pro Asn Ile Ile Arg Leu Glu Gly Val Val Thr Lys Ser
690 695 700

Arg Pro Val Met Ile Leu Thr Glu Phe Met Glu Asn Cys Ala Leu Asp
705 710 715 720

Ser Phe Leu Arg Leu Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val
725 730 735

Gly Met Leu Arg Gly Ile Ala Ala Gly Met Lys Tyr Leu Ser Glu Met
740 745 750

Asn Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser
755 760 765

Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Phe Leu Glu
770 775 780

```
Asp Asp Pro Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly Gly Lys Ile
785                 790                 795                 800

Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Ala Tyr Arg Lys Phe Thr
                805                 810                 815

Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met
            820                 825                 830

Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile
        835                 840                 845

Asn Ala Val Glu Gln Asp Tyr Arg Leu Pro Pro Pro Met Asp Cys Pro
    850                 855                 860

Thr Ala Leu His Gln Leu Met Leu Asp Cys Trp Val Arg Asp Arg Asn
865                 870                 875                 880

Leu Arg Pro Lys Phe Ser Gln Ile Val Asn Thr Leu Asp Lys Leu Ile
                885                 890                 895

Arg Asn Ala Ala Ser Leu Lys Val Ile Ala Ser Ala Gln Ser Gly Met
            900                 905                 910

Ser Gln Pro Leu Leu Asp Arg Thr Val Pro Asp Tyr Thr Thr Phe Thr
        915                 920                 925

Thr Val Gly Asp Trp Leu Asp Ala Ile Lys Met Gly Arg Tyr Lys Glu
    930                 935                 940

Ser Phe Val Ser Ala Gly Phe Ala Ser Phe Asp Leu Val Ala Gln Met
945                 950                 955                 960

Thr Ala Glu Asp Leu Leu Arg Ile Gly Val Thr Leu Ala Gly His Gln
                965                 970                 975

Lys Lys Ile Leu Ser Ser Ile Gln Asp Met Arg Leu Gln Met Asn Gln
            980                 985                 990

Thr Leu Pro Val Gln Val
        995
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 983 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

```
Met Asp Cys Gln Leu Ser Ile Leu Leu Leu Leu Ser Cys Ser Val Leu
1               5                   10                  15
```

```
Asp Ser Phe Gly Glu Leu Ile Pro Gln Pro Ser Asn Glu Val Asn Leu
            20                  25                  30

Leu Asp Ser Lys Thr Ile Gln Gly Glu Leu Gly Trp Ile Ser Tyr Pro
        35                  40                  45

Ser His Gly Trp Glu Glu Ile Ser Gly Val Asp Glu His Tyr Thr Pro
    50                  55                  60

Ile Arg Thr Tyr Gln Val Cys Asn Val Met Asp His Ser Gln Asn Asn
65                  70                  75                  80

Trp Leu Arg Thr Asn Trp Val Pro Arg Asn Ser Ala Gln Lys Ile Tyr
                85                  90                  95

Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn Ser Ile Pro Leu Val
            100                 105                 110

Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr Tyr Met Glu Ser Asp
        115                 120                 125

Asp Asp His Gly Val Lys Phe Arg Glu His Gln Phe Thr Lys Ile Asp
    130                 135                 140

Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Met Asp Leu Gly Asp Arg
145                 150                 155                 160

Ile Leu Lys Leu Asn Thr Glu Ile Arg Glu Val Gly Pro Val Asn Lys
                165                 170                 175

Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly Ala Cys Val Ala Leu
            180                 185                 190

Val Ser Val Arg Val Tyr Phe Lys Lys Cys Pro Phe Thr Val Lys Asn
        195                 200                 205

Leu Ala Met Phe Pro Asp Thr Val Pro Met Asp Ser Gln Ser Leu Val
    210                 215                 220

Glu Val Arg Gly Ser Cys Val Asn Asn Ser Lys Glu Glu Asp Pro Pro
225                 230                 235                 240

Arg Met Tyr Cys Ser Thr Glu Gly Glu Trp Leu Val Pro Ile Gly Lys
                245                 250                 255

Cys Ser Cys Asn Ala Gly Tyr Glu Glu Arg Gly Phe Met Cys Gln Ala
            260                 265                 270

Cys Arg Pro Gly Phe Tyr Lys Ala Leu Asp Gly Asn Met Lys Cys Ala
        275                 280                 285

Lys Cys Pro Pro His Ser Ser Thr Gln Glu Asp Gly Ser Met Asn Cys
    290                 295                 300

Arg Cys Glu Asn Asn Tyr Phe Arg Ala Asp Lys Asp Pro Pro Ser Met
305                 310                 315                 320
```

```
Ala Cys Thr Arg Pro Pro Ser Ser Pro Arg Asn Val Ile Ser Asn Ile
                325                 330                 335

Asn Glu Thr Ser Val Ile Leu Asp Trp Ser Trp Pro Leu Asp Thr Gly
            340                 345                 350

Gly Arg Lys Asp Val Thr Phe Asn Ile Ile Cys Lys Lys Cys Gly Trp
        355                 360                 365

Asn Ile Lys Gln Cys Glu Pro Cys Ser Pro Asn Val Arg Phe Leu Pro
    370                 375                 380

Arg Gln Phe Gly Leu Thr Asn Thr Thr Val Thr Val Thr Asp Leu Leu
385                 390                 395                 400

Ala His Thr Asn Tyr Thr Phe Glu Ile Asp Ala Val Asn Gly Val Ser
                405                 410                 415

Glu Leu Ser Ser Pro Pro Arg Gln Phe Ala Ala Val Ser Ile Thr Thr
            420                 425                 430

Asn Gln Ala Ala Pro Ser Pro Val Leu Thr Ile Lys Lys Asp Arg Thr
        435                 440                 445

Ser Arg Asn Ser Ile Ser Leu Ser Trp Gln Glu Pro Glu His Pro Asn
    450                 455                 460

Gly Ile Ile Leu Asp Tyr Glu Val Lys Tyr Tyr Glu Lys Gln Glu Gln
465                 470                 475                 480

Glu Thr Ser Tyr Thr Ile Leu Arg Ala Arg Gly Thr Asn Val Thr Ile
                485                 490                 495

Ser Ser Leu Lys Pro Asp Thr Ile Tyr Val Leu Gln Ile Arg Ala Arg
            500                 505                 510

Thr Ala Ala Gly Tyr Gly Thr Asn Ser Arg Lys Phe Glu Phe Glu Thr
        515                 520                 525

Ser Pro Asp Ser Phe Ser Ile Ser Gly Glu Ser Ser Gln Val Val Met
    530                 535                 540

Ile Ala Ile Ser Ala Ala Val Ala Ile Ile Leu Leu Thr Val Val Ile
545                 550                 555                 560

Tyr Val Leu Ile Gly Arg Phe Cys Gly Tyr Lys Ser Lys His Gly Ala
                565                 570                 575

Asp Glu Lys Arg Leu His Phe Gly Asn Gly His Leu Lys Leu Pro Gly
            580                 585                 590

Leu Arg Thr Tyr Val Asp Pro His Thr Tyr Glu Asp Pro Thr Gln Ala
        595                 600                 605

Val His Glu Phe Ala Lys Glu Leu Asp Ala Thr Asn Ile Ser Ile Asp
    610                 615                 620
```

Lys Val Val Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu
625 630 635 640

Lys Leu Pro Ser Lys Lys Glu Ile Ser Val Ala Ile Lys Thr Leu Lys
645 650 655

Val Gly Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Gly Glu Ala Ser
660 665 670

Ile Met Gly Gln Phe Asp His Pro Asn Ile Ile Arg Leu Glu Gly Val
675 680 685

Val Thr Lys Ser Lys Pro Val Met Ile Val Thr Glu Tyr Met Glu Asn
690 695 700

Gly Ser Leu Asp Ser Phe Leu Arg Lys His Asp Ala Gln Phe Thr Val
705 710 715 720

Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ser Gly Met Lys Tyr
725 730 735

Leu Ser Asp Met Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile
740 745 750

Leu Ile Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser
755 760 765

Arg Val Leu Glu Asp Asp Pro Glu Ala Ala Tyr Thr Thr Arg Gly Gly
770 775 780

Lys Ile Pro Ile Arg Trp Thr Ser Pro Glu Ala Ile Ala Tyr Arg Lys
785 790 795 800

Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Leu Trp Glu
805 810 815

Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Glu Met Ser Asn Gln Asp
820 825 830

Val Ile Lys Ala Val Asp Glu Gly Tyr Arg Leu Pro Pro Pro Met Asp
835 840 845

Cys Pro Ala Ala Leu Tyr Gln Leu Met Leu Asp Cys Trp Gln Lys Asp
850 855 860

Arg Asn Asn Arg Pro Lys Phe Glu Gln Ile Val Ser Ile Leu Asp Lys
865 870 875 880

Leu Ile Arg Asn Pro Gly Ser Leu Lys Ile Ile Thr Ser Ala Ala Ala
885 890 895

Arg Pro Ser Asn Leu Leu Leu Asp Gln Ser Asn Val Asp Ile Ser Thr
900 905 910

Phe Arg Thr Thr Gly Asp Trp Leu Asn Gly Val Arg Thr Ala His Cys
915 920 925

Lys Glu Ile Phe Thr Gly Val Glu Tyr Ser Ser Cys Asp Thr Ile Ala
930 935 940

Lys Ile Ser Thr Asp Asp Met Lys Lys Val Gly Val Thr Val Val Gly
945 950 955 960

Pro Gln Lys Lys Ile Ile Ser Ser Ile Lys Ala Leu Glu Thr Gln Ser
965 970 975

Lys Asn Gly Pro Val Pro Val
980

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CTGCTCGCCG CCGTGGAAGA AACG 24

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 39 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GCGTCTAGAT TATCACTTCT CCTGGATGCT TGTCTGGTA 39

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GCGGACGCCG CCGCCATGGC CCTGGATTGC CTGCTGCTGT TCCTCCTG 48

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CGTTTCTTCC ACGGCGGCGA GCAGAGATGC CAGGAGGAAC AGCAGCAGGC AATC 54

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met Ala Leu Asp Cys Leu Leu Leu Phe Leu Leu Ala Ser
1 5 10

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

AGGGAATTCC AYCGNGAYYT NGCNGC 26

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

AGGGGATCCR WARSWCCANA CRTC 24

WHAT IS CLAIMED IS:

1. An isolated nucleic acid encoding a polypeptide having at least one of the biological activities of an EPH-like receptor protein tyrosine kinase, the nucleic acid selected from the group consisting of:

(a) the nucleic acids set forth in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16 and their complementary strands;

(b) a nucleic acid hybridizing to the coding regions of the nucleic acids in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16; and

(c) a nucleic acid of (b) which, but for the degeneracy of the genetic code, would hybridize to the coding regions of the nucleic acids in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16.

2. A polypeptide product of expression of a nucleic acid of Claim 1 in a procaryotic or eucaryotic host cell.

3. A nucleic acid of Claim 1 which is of human origin.

4. A nucleic acid of Claim 1 which encodes a polypeptide having part or all of the amino acid sequence as shown in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16.

5. A nucleic acid of Claim 1 encoding a fragment comprising an EPH-like receptor extracellular domain.

6. A nucleic acid of Claim 1 which is cDNA, genomic DNA, synthetic DNA or RNA.

7. A nucleic acid of Claim 1 which includes one or more codons preferred for expression in E. coli host cells.

8. A nucleic acid of Claim 1 which includes one or more codon preferred for expression in mammalian cells.

9. A nucleic acid encoding amino acids 6-524 as set forth in SEQ ID NO: 10, and optionally encoding an amino terminal methionyl residue.

10. A nucleic acid encoding amino acids 1-547 as set forth in SEQ ID NO: 12, and optionally encoding an amino acid terminal methionyl residue.

11. A nucleic acid encoding amino acids 21-547 as set forth in SEQ ID NO: 14, and optionally encoding an amino terminal methionyl residue.

12. A nucleic acid encoding amino acids 23-553 as set forth in SEQ ID NO: 16, and optionally encoding an amino terminal methionyl residue.

13. A nucleic acid encoding a chimeric protein, wherein the protein comprises an EPH-like receptor extracellular domain fused to a heterologous receptor cytoplasmic domain.

14. A nucleic acid of Claim 13 wherein the extracellular domain is selected from the group consisting of HEK5, HEK7, HEK8 and HEK11 extracellular domains.

15. A biologically functional plasmid or viral DNA vector including a nucleic acid of Claim 1.

16. A procaryotic or eucaryotic host cell stably transformed or transfected with the plasmid of Claim 15.

17. A method of producing an EPH-like receptor protein tyrosine kinase comprising culturing the host cell of Claim 16 to allow the host cell to express the EPH-like receptor protein tyrosine kinase.

18. An isolated polypeptide having an amino acid sequence as shown in any of SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14 or SEQ ID NO: 16, or a fragment or analog thereof, wherein the polypeptide has at least one of the biological activities of an EPH-like receptor protein tyrosine kinase.

19. Purified and isolated HEK5 receptor.

20. Purified and isolated HEK7 receptor.

21. Purified and isolated HEK8 receptor.

22. Purified and isolated HEK11 receptor.

23. A polypeptide of Claim 18 wherein the biological activity is the binding of a ligand.

24. A polypeptide of Claim 18 which is of human origin.

25. A polypeptide of Claims 18 characterized by being the product of procaryotic or eucaryotic expression of an exogenous DNA sequence.

26. A polypeptide of Claim 25 wherein the exogenous DNA is a cDNA.

27. A polypeptide of Claim 25 wherein the exogenous DNA is a genomic DNA.

28. An antibody or fragment thereof specifically binding a polypeptide of Claim 18.

29. An antibody of Claim 28 which is a monoclonal antibody.

30. A pharmaceutical composition comprising a therapeutically effective amount of a polypeptide of Claim 18 in a mixture with a pharmaceutically acceptable adjuvant, carrier, solubilizer or diluent.

31. A pharmaceutical composition comprising a therapeutically effective amount of an antibody of Claim 28 in a mixture with a pharmaceutically acceptable adjuvant, carrier, solubilizer or diluent.

32. A method for modulating the endogenous activation of an EPH-like receptor protein tyrosine kinase comprising administering an effective amount of a polypeptide of Claim 18.

33. A method for modulating the synthesis of an EPH-like receptor protein tyrosine kinase comprising hybridizing an antisense oligonucleotide to a nucleic acid of Claim 1.

34. A method of identifying a ligand that binds to a receptor polypeptide of Claim 18 comprising the steps of:

a) exposing at least one molecule to the receptor polypeptide for a time sufficient to allow formation of a receptor/ligand complex;

b) removing non-complexed molecules; and

c) detecting the presence of the molecule bound to the receptor polypeptide.

FIG. 1A

```
CTG CTC GCC GCC GTG GAA GAA ACG CTA ATG GAC TCC ACT ACA GCG ACT        48
Leu Leu Ala Ala Val Glu Glu Thr Leu Met Asp Ser Thr Thr Ala Thr
 1               5                  10                  15

GCT GAG CTG GGC TGG ATG GTG CAT CCT CCA TCA GGG TGG GAA GAG GTG        96
Ala Glu Leu Gly Trp Met Val His Pro Pro Ser Gly Trp Glu Glu Val
            20                  25                  30

AGT GGC TAC GAT GAG AAC ATG AAC ACG ATC CGC ACG TAC CAG GTG TGC       144
Ser Gly Tyr Asp Glu Asn Met Asn Thr Ile Arg Thr Tyr Gln Val Cys
        35                  40                  45

AAC GTG TTT GAG TCA AGC CAG AAC AAC TGG CTA CGG ACC AAG TTT ATC       192
Asn Val Phe Glu Ser Ser Gln Asn Asn Trp Leu Arg Thr Lys Phe Ile
    50                  55                  60

CGG CGC CGT GGG GCC CAC CGC ATC CAC GTG GAG ATG AAG TTT TCG GTG       240
Arg Arg Arg Gly Ala His Arg Ile His Val Glu Met Lys Phe Ser Val
65                  70                  75                  80

CGT GAC TGC AGC AGC ATC CCC AGC GTG CCT GGC TCC TGC AAG GAG ACC       288
Arg Asp Cys Ser Ser Ile Pro Ser Val Pro Gly Ser Cys Lys Glu Thr
                85                  90                  95

TTC AAC CTC TAT TAC TAT GAG GCT GAC TTT GAC TCG GCC ACC AAG ACC       336
Phe Asn Leu Tyr Tyr Tyr Glu Ala Asp Phe Asp Ser Ala Thr Lys Thr
            100                 105                 110

TTC CCC AAC TGG ATG GAG AAT CCA TGG GTG AAG GTG GAT ACC ATT GCA       384
Phe Pro Asn Trp Met Glu Asn Pro Trp Val Lys Val Asp Thr Ile Ala
        115                 120                 125

GCC GAC GAG AGC TTC TCC CAG GTG GAC CTG GGT GGC CGC GTC ATG AAA       432
Ala Asp Glu Ser Phe Ser Gln Val Asp Leu Gly Gly Arg Val Met Lys
    130                 135                 140

ATC AAC ACC GAG GTG CGG AGC TTC GGA CCT GTG TCC CGC AGC GGC TTC       480
Ile Asn Thr Glu Val Arg Ser Phe Gly Pro Val Ser Arg Ser Gly Phe
145                 150                 155                 160

TAC CTG GCC TTC CAG GAC TAT GGC GGC TGC ATG TCC CTC ATC GCC GTG       528
Tyr Leu Ala Phe Gln Asp Tyr Gly Gly Cys Met Ser Leu Ile Ala Val
                165                 170                 175

CGT GTC TTC TAC CGC AAG TGC CCC CGC ATC ATC CAG AAT GGC GCC ATC       576
Arg Val Phe Tyr Arg Lys Cys Pro Arg Ile Ile Gln Asn Gly Ala Ile
            180                 185                 190
```

FIG. 1B

```
TTC CAG GAA ACC CTG TCG GGG GCT GAG AGC ACA TCG CTG GTG GCT GCC          624
Phe Gln Glu Thr Leu Ser Gly Ala Glu Ser Thr Ser Leu Val Ala Ala
        195                 200                 205

CGG GGC AGC TGC ATC GCC AAT GCG GAA GAG GTG GAT GTA CCC ATC AAG          672
Arg Gly Ser Cys Ile Ala Asn Ala Glu Glu Val Asp Val Pro Ile Lys
    210                 215                 220

CTC TAC TGT AAC GGG GAC GGC GAG TGG CTG GTG CCC ATC GGG CGC TGC          720
Leu Tyr Cys Asn Gly Asp Gly Glu Trp Leu Val Pro Ile Gly Arg Cys
225                 230                 235                 240

ATG TGC AAA GCA GGC TTC GAG GCC GTT GAG AAT GGC ACC GTC TGC CGA          768
Met Cys Lys Ala Gly Phe Glu Ala Val Glu Asn Gly Thr Val Cys Arg
                245                 250                 255

GGT TGT CCA TCT GGG ACT TTC AAG GCC AAC CAA GGG GAT GAG GCC TGT          816
Gly Cys Pro Ser Gly Thr Phe Lys Ala Asn Gln Gly Asp Glu Ala Cys
            260                 265                 270

ACC CAC TGT CCC ATC AAC AGC CGG ACC ACT TCT GAA GGG GCC ACC AAC          864
Thr His Cys Pro Ile Asn Ser Arg Thr Thr Ser Glu Gly Ala Thr Asn
        275                 280                 285

TGT GTC TGC CGC AAT GGC TAC TAC AGA GCA GAC CTG GAC CCC CTG GAC          912
Cys Val Cys Arg Asn Gly Tyr Tyr Arg Ala Asp Leu Asp Pro Leu Asp
    290                 295                 300

ATG CCC TGC ACA ACC ATC CCC TCC GCG CCC CAG GCT GTG ATT TCC AGT          960
Met Pro Cys Thr Thr Ile Pro Ser Ala Pro Gln Ala Val Ile Ser Ser
305                 310                 315                 320

GTC AAT GAG ACC TCC CTC ATG CTG GAG TGG ACC CCT CCC CGC GAC TCC         1008
Val Asn Glu Thr Ser Leu Met Leu Glu Trp Thr Pro Pro Arg Asp Ser
                325                 330                 335

GGA GGC CGA GAG GAC CTC GTC TAC AAC ATC ATC TGC AAG AGC TGT GGC         1056
Gly Gly Arg Glu Asp Leu Val Tyr Asn Ile Ile Cys Lys Ser Cys Gly
            340                 345                 350

TCG GGC CGG GGT GCC TGC ACC CGC TGC GGG GAC AAT GTA CAG TAC GCA         1104
Ser Gly Arg Gly Ala Cys Thr Arg Cys Gly Asp Asn Val Gln Tyr Ala
        355                 360                 365

CCA CGC CAG CTA GGC CTG ACC GAG CCA CGC ATT TAC ATC AGT GAC CTG         1152
Pro Arg Gln Leu Gly Leu Thr Glu Pro Arg Ile Tyr Ile Ser Asp Leu
    370                 375                 380

CTG GCC CAC ACC CAG TAC ACC TTC GAG ATC CAG GCT GTG AAC GGC GTT         1200
Leu Ala His Thr Gln Tyr Thr Phe Glu Ile Gln Ala Val Asn Gly Val
385                 390                 395                 400
```

FIG. IC

```
ACT GAC CAG AGC CCC TTC TCG CCT CAG TTC GCC TCT GTG AAC ATC ACC      1248
Thr Asp Gln Ser Pro Phe Ser Pro Gln Phe Ala Ser Val Asn Ile Thr
                405                 410                 415

ACC AAC CAG GCA GCT CCA TCG GCA GTG TCC ATC ATG CAT CAG GTG AGC      1296
Thr Asn Gln Ala Ala Pro Ser Ala Val Ser Ile Met His Gln Val Ser
            420                 425                 430

CGC ACC GTG GAC AGC ATT ACC CTG TCG TGG TCC CAG CCG GAC CAG CCC      1344
Arg Thr Val Asp Ser Ile Thr Leu Ser Trp Ser Gln Pro Asp Gln Pro
        435                 440                 445

AAT GGC GTG ATC CTG GAC TAT GAG CTG CAG TAC TAT GAG AAG GAG CTC      1392
Asn Gly Val Ile Leu Asp Tyr Glu Leu Gln Tyr Tyr Glu Lys Glu Leu
    450                 455                 460

AGT GAG TAC AAC GCC ACA GCC ATA AAA AGC CCC ACC AAC ACG GTC ACG      1440
Ser Glu Tyr Asn Ala Thr Ala Ile Lys Ser Pro Thr Asn Thr Val Thr
465                 470                 475                 480

GGC CTC AAA GCC GGC GCC ATC TAT GTC TTC CAG GTG CGG GCA CGC ACT      1488
Gly Leu Lys Ala Gly Ala Ile Tyr Val Phe Gln Val Arg Ala Arg Thr
                485                 490                 495

GTG GCA GGC TAC GGG CGC TAC AGC GGC AAG ATG TAC TTC CAG ACC ATG      1536
Val Ala Gly Tyr Gly Arg Tyr Ser Gly Lys Met Tyr Phe Gln Thr Met
            500                 505                 510

ACA GAA GCC GAG TAC CAG ACA AGC ATC CAG GAG AAG TTG CCA CTC ATC      1584
Thr Glu Ala Glu Tyr Gln Thr Ser Ile Gln Glu Lys Leu Pro Leu Ile
        515                 520                 525

ATC GGC TCC TCG GCC GCT GGC CTG GTC TTC CTC ATT GCT GTG GTT GTC      1632
Ile Gly Ser Ser Ala Ala Gly Leu Val Phe Leu Ile Ala Val Val Val
    530                 535                 540

ATC GCC ATC GTG TGT AAC AGA CGG GGG TTT GAG CGT GCT GAC TCG GAG      1680
Ile Ala Ile Val Cys Asn Arg Arg Gly Phe Glu Arg Ala Asp Ser Glu
545                 550                 555                 560

TAC ACG GAC AAG CTG CAA CAC TAC ACC AGT GGC CAC ATA ACC CCA GGC      1728
Tyr Thr Asp Lys Leu Gln His Tyr Thr Ser Gly His Ile Thr Pro Gly
                565                 570                 575

ATG AAG ATC TAC ATC GAT CCT TTC ACC TAC GAG GAC CCC AAC GAG GCA      1776
Met Lys Ile Tyr Ile Asp Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala
            580                 585                 590

GTG CGG GAG TTT GCC AAG GAA ATT GAC ATC TCC TGT GTC AAA ATT GAG      1824
Val Arg Glu Phe Ala Lys Glu Ile Asp Ile Ser Cys Val Lys Ile Glu
        595                 600                 605
```

FIG. 1D

```
CAG GTG ATC GGA GCA GGG GAG TTT GGC GAG GTC TGC AGT GGC CAC CTG      1872
Gln Val Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly His Leu
    610                 615                 620

AAG CTG CCA GGC AAG AGA GAG ATC TTT GTG GCC ATC AAG ACG CTC AAG      1920
Lys Leu Pro Gly Lys Arg Glu Ile Phe Val Ala Ile Lys Thr Leu Lys
625                 630                 635                 640

TCG GGC TAC ACG GAG AAG CAG CGC CGG GAC TTC CTG AGC GAA GCC TCC      1968
Ser Gly Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Ser Glu Ala Ser
                645                 650                 655

ATC ATG GGC CAG TTC GAC CAT CCC AAC GTC ATC CAC CTG GAG GGT GTC      2016
Ile Met Gly Gln Phe Asp His Pro Asn Val Ile His Leu Glu Gly Val
            660                 665                 670

GTG ACC AAG AGC ACA CCT GTG ATG ATC ATC ACC GAG TTC ATG GAG AAT      2064
Val Thr Lys Ser Thr Pro Val Met Ile Ile Thr Glu Phe Met Glu Asn
        675                 680                 685

GGC TCC CTG GAC TCC TTT CTC CGG CAA AAC GAT GGG CAG TTC ACA GTC      2112
Gly Ser Leu Asp Ser Phe Leu Arg Gln Asn Asp Gly Gln Phe Thr Val
    690                 695                 700

ATC CAG CTG GTG GGC ATG CTT CGG GGC ATC GCA GCT GGC ATG AAG TAC      2160
Ile Gln Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Lys Tyr
705                 710                 715                 720

CTG GCA GAC ATG AAC TAT GTT CAC CGT GAC CTG GCT GCC CGC AAC ATC      2208
Leu Ala Asp Met Asn Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile
                725                 730                 735

CTC GTC AAC AGC AAC CTG GTC TGC AAG GTG TCG GAC TTT GGG CTC TCA      2256
Leu Val Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser
            740                 745                 750

CGC TTT CTA GAG GAC GAT ACC TCA GAC CCC ACC TAC ACC AGT GCC CTG      2304
Arg Phe Leu Glu Asp Asp Thr Ser Asp Pro Thr Tyr Thr Ser Ala Leu
        755                 760                 765

GGC GGA AAG TTC CCC ATC CGC TGG ACA GCC CCG GAA GCC ATC CAG TAC      2352
Gly Gly Lys Phe Pro Ile Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr
    770                 775                 780

CGG AAG TTC ACC TCG GCC AGT GAT GTG TGG AGC TAC GGC ATT GTC ATG      2400
Arg Lys Phe Thr Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met
785                 790                 795                 800

TGG GAG GTG ATG TCC TAT GGG GAG CGG CCC TAC TGG GAC ATG ACC AAC      2448
Trp Glu Val Met Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Thr Asn
                805                 810                 815
```

FIG. IE

```
CAG GAT GTA ATC AAT GCC ATT GAG CAG GAC TAT CGG CTG CCA CCG CCC      2496
Gln Asp Val Ile Asn Ala Ile Glu Gln Asp Tyr Arg Leu Pro Pro Pro
          820                 825                 830

ATG GAC TGC CCG AGC GCC CTG CAC CAA CTC ATG CTG GAC TGT TGG CAG      2544
Met Asp Cys Pro Ser Ala Leu His Gln Leu Met Leu Asp Cys Trp Gln
        835                 840                 845

AAG GAC CGC AAC CAC CGG CCC AAG TTC GGC CAA ATT GTC AAC ACG CTA      2592
Lys Asp Arg Asn His Arg Pro Lys Phe Gly Gln Ile Val Asn Thr Leu
    850                 855                 860

GAC AAG ATG ATC CGC AAT CCC AAC AGC CTC AAA GCC ATG GCG CCC CTC      2640
Asp Lys Met Ile Arg Asn Pro Asn Ser Leu Lys Ala Met Ala Pro Leu
865                 870                 875                 880

TCC TCT GGC ATC AAC CTG CCG CTG CTG GAC CGC ACG ATC CCC GAC TAC      2688
Ser Ser Gly Ile Asn Leu Pro Leu Leu Asp Arg Thr Ile Pro Asp Tyr
                885                 890                 895

ACC AGC TTT AAC ACG GTG GAC GAG TGG CTG GAG GCC ATC AAG ATG GGG      2736
Thr Ser Phe Asn Thr Val Asp Glu Trp Leu Glu Ala Ile Lys Met Gly
            900                 905                 910

CAG TAC AAG GAG AGC TTC GCC AAT GCC GGC TTC ACC TCC TTT GAC GTC      2784
Gln Tyr Lys Glu Ser Phe Ala Asn Ala Gly Phe Thr Ser Phe Asp Val
        915                 920                 925

GTG TCT CAG ATG ATG ATG GAG GAC ATT CTC CGG GTT GGG GTC ACT TTG      2832
Val Ser Gln Met Met Met Glu Asp Ile Leu Arg Val Gly Val Thr Leu
    930                 935                 940

GCT GGC CAC CAG AAA AAA ATC CTG AAC AGT ATC CAG GTG ATG CGG GCG      2880
Ala Gly His Gln Lys Lys Ile Leu Asn Ser Ile Gln Val Met Arg Ala
945                 950                 955                 960

CAG ATG AAC CAG ATT CAG TCT GTG GAG GTT TGACATTCAC CTGCCTCGGC        2930
Gln Met Asn Gln Ile Gln Ser Val Glu Val
                965                 970

TCACCTCTTC CTCCAAGCCC CGCCCCCTCT GC                                  2962
```

FIG. 2A

```
CCA GCG TCC CTG GCC GGC TGC TAC TCT GCA CCT CGA CGG GCT CCC CTC          48
Pro Ala Ser Leu Ala Gly Cys Tyr Ser Ala Pro Arg Arg Ala Pro Leu
 1               5                  10                  15

TGG ACG TGC CTT CTC CTG TGC GCC GCA CTC CGG ACC CTC CTG GCC AGC          96
Trp Thr Cys Leu Leu Leu Cys Ala Ala Leu Arg Thr Leu Leu Ala Ser
            20                  25                  30

CCC AGC AAC GAA GTG AAT TTA TTG GAT TCA CGC ACT GTC ATG GGG GAC         144
Pro Ser Asn Glu Val Asn Leu Leu Asp Ser Arg Thr Val Met Gly Asp
        35                  40                  45

CTG GGA TGG ATT GCT TTT CCA AAA AAT GGG TGG GAA GAG ATT GGT GAA         192
Leu Gly Trp Ile Ala Phe Pro Lys Asn Gly Trp Glu Glu Ile Gly Glu
    50                  55                  60

GTG GAT GAA AAT TAT GCC CCT ATC CAC ACA TAC CAA GTA TGC AAA GTG         240
Val Asp Glu Asn Tyr Ala Pro Ile His Thr Tyr Gln Val Cys Lys Val
65                  70                  75                  80

ATG GAA CAG AAT CAG AAT AAC TGG CTT TTG ACC AGT TGG ATC TCC AAT         288
Met Glu Gln Asn Gln Asn Asn Trp Leu Leu Thr Ser Trp Ile Ser Asn
                85                  90                  95

GAA GGT GCT TCC AGA ATC TTC ATA GAA CTC AAA TTT ACC CTG CGG GAC         336
Glu Gly Ala Ser Arg Ile Phe Ile Glu Leu Lys Phe Thr Leu Arg Asp
            100                 105                 110

TGC AAC AGC CTT CCT GGA GGA CTG GGG ACC TGT AAG GAA ACC TTT AAT         384
Cys Asn Ser Leu Pro Gly Gly Leu Gly Thr Cys Lys Glu Thr Phe Asn
        115                 120                 125

ATG TAT TAC TTT GAG TCA GAT GAT CAG AAT GGG AGA AAC ATC AAG GAA         432
Met Tyr Tyr Phe Glu Ser Asp Asp Gln Asn Gly Arg Asn Ile Lys Glu
    130                 135                 140

AAC CAA TAC ATC AAA ATT GAT ACC ATT GCT GCC GAT GAA AGC TTT ACA         480
Asn Gln Tyr Ile Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr
145                 150                 155                 160

GAA CTT GAT CTT GGT GAC CGT GTT ATG AAA CTG AAT ACA GAG GTC AGA         528
Glu Leu Asp Leu Gly Asp Arg Val Met Lys Leu Asn Thr Glu Val Arg
                165                 170                 175

GAT GTA GGA CCT CTA AGC AAA AAG GGA TTT TAT CTT GCT TTT CAA GAT         576
Asp Val Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp
            180                 185                 190

GTT GGT GCT TGC ATT GCT CTG GTT TCT GTG CGT GTA TAC TAT AAA AAA         624
Val Gly Ala Cys Ile Ala Leu Val Ser Val Arg Val Tyr Tyr Lys Lys
        195                 200                 205
```

FIG. 2B

```
TGC CCT TCT GTG GTA CGA CAC TTG GCT GTC TTC CCT GAC ACC ATC ACT      672
Cys Pro Ser Val Val Arg His Leu Ala Val Phe Pro Asp Thr Ile Thr
    210                 215                 220

GGA GCT GAT TCT TCC CAA TTG CTC GAA GTG TCG GGC TCC TGT GTC AAC      720
Gly Ala Asp Ser Ser Gln Leu Leu Glu Val Ser Gly Ser Cys Val Asn
225                 230                 235                 240

CAT TCT GTG ACC GAT GAA CCT CCC AAA ATG CAC TGC AGC GCC GAA GGG      768
His Ser Val Thr Asp Glu Pro Pro Lys Met His Cys Ser Ala Glu Gly
                245                 250                 255

GAG TGG CTG GTG CCC ATC GGG AAA TGC ATG TGC AAG GCA GGA TAT GAA      816
Glu Trp Leu Val Pro Ile Gly Lys Cys Met Cys Lys Ala Gly Tyr Glu
            260                 265                 270

GAG AAA AAT GGC ACC TGT CAA GTG TGC AGA CCT GGG TTC TTC AAA GCC      864
Glu Lys Asn Gly Thr Cys Gln Val Cys Arg Pro Gly Phe Phe Lys Ala
        275                 280                 285

TCA CCT CAC ATC CAG AGC TGC GGC AAA TGT CCA CCT CAC AGT TAT ACC      912
Ser Pro His Ile Gln Ser Cys Gly Lys Cys Pro Pro His Ser Tyr Thr
    290                 295                 300

CAT GAG GAA GCT TCA ACC TCT TGT GTC TGT GAA AAG GAT TAT TTC AGG      960
His Glu Glu Ala Ser Thr Ser Cys Val Cys Glu Lys Asp Tyr Phe Arg
305                 310                 315                 320

AGA GAG TCT GAT CCA CCC ACA ATG GCA TGC ACA AGA CCC CCC TCT GCT     1008
Arg Glu Ser Asp Pro Pro Thr Met Ala Cys Thr Arg Pro Pro Ser Ala
                325                 330                 335

CCT CGG AAT GCC ATC TCA AAT GTT AAT GAA ACT AGT GTC TTT CTG GAA     1056
Pro Arg Asn Ala Ile Ser Asn Val Asn Glu Thr Ser Val Phe Leu Glu
            340                 345                 350

TGG ATT CCG CCT GCT GAC ACT GGT GGA AGG AAA GAC GTG TCA TAT TAT     1104
Trp Ile Pro Pro Ala Asp Thr Gly Gly Arg Lys Asp Val Ser Tyr Tyr
        355                 360                 365

ATT GCA TGC AAG AAG TGC AAC TCC CAT GCA GGT GTG TGT GAG GAG TGT     1152
Ile Ala Cys Lys Lys Cys Asn Ser His Ala Gly Val Cys Glu Glu Cys
    370                 375                 380

GGC GGT CAT GTC AGG TAC CTT CCC CGG CAA AGC GGC CTG AAA AAC ACC     1200
Gly Gly His Val Arg Tyr Leu Pro Arg Gln Ser Gly Leu Lys Asn Thr
385                 390                 395                 400

TCT GTC ATG ATG GTG GAT CTA CTC GCT CAC ACA AAC TAT ACC TTT GAG     1248
Ser Val Met Met Val Asp Leu Leu Ala His Thr Asn Tyr Thr Phe Glu
                405                 410                 415
```

FIG. 2C

```
ATT GAG GCA GTG AAT GGA GTG TCC GAC TTG AGC CCA GGA GCC CGG CAG      1296
Ile Glu Ala Val Asn Gly Val Ser Asp Leu Ser Pro Gly Ala Arg Gln
            420                 425                 430

TAT GTG TCT GTA AAT GTA ACC ACA AAT CAA GCA GCT CCA TCT CCA GTC      1344
Tyr Val Ser Val Asn Val Thr Thr Asn Gln Ala Ala Pro Ser Pro Val
        435                 440                 445

ACC AAT GTG AAA AAA GGG AAA ATT GCA AAA AAC AGC ATC TCT TTG TCT      1392
Thr Asn Val Lys Lys Gly Lys Ile Ala Lys Asn Ser Ile Ser Leu Ser
    450                 455                 460

TGG CAA GAA CCA GAT CGT CCC AAT GGA ATC ATC CTA GAG TAT GAA ATC      1440
Trp Gln Glu Pro Asp Arg Pro Asn Gly Ile Ile Leu Glu Tyr Glu Ile
465                 470                 475                 480

AAG CAT TTT GAA AAG GAC CAA GAG ACC AGC TAC ACG ATT ATC AAA TCT      1488
Lys His Phe Glu Lys Asp Gln Glu Thr Ser Tyr Thr Ile Ile Lys Ser
                485                 490                 495

AAA GAG ACA ACT ATT ACT GCA GAG GGC TTG AAA CCA GCT TCA GTT TAT      1536
Lys Glu Thr Thr Ile Thr Ala Glu Gly Leu Lys Pro Ala Ser Val Tyr
            500                 505                 510

GTC TTC CAA ATT CGA GCA CGT ACA GCA GCA GGC TAT GGT GTC TTC AGT      1584
Val Phe Gln Ile Arg Ala Arg Thr Ala Ala Gly Tyr Gly Val Phe Ser
        515                 520                 525

CGA AGA TTT GAG TTT GAA ACC ACC CCA GTG TTT GCA GCA TCC AGC GAT      1632
Arg Arg Phe Glu Phe Glu Thr Thr Pro Val Phe Ala Ala Ser Ser Asp
    530                 535                 540

CAA AGC CAG ATT CCT GTA ATT GCT GTG TCT GTG ACA GTA GGA GTC ATT      1680
Gln Ser Gln Ile Pro Val Ile Ala Val Ser Val Thr Val Gly Val Ile
545                 550                 555                 560

TTG TTG GCA GTG GTT ATC GGC GTC CTC CTC AGT GGA AGG CGG TGT GGC      1728
Leu Leu Ala Val Val Ile Gly Val Leu Leu Ser Gly Arg Arg Cys Gly
                565                 570                 575

TAC AGC AAA GCA AAA CAA GAT CCA GAA GAG GAA AAG ATG CAT TTT CAT      1776
Tyr Ser Lys Ala Lys Gln Asp Pro Glu Glu Glu Lys Met His Phe His
            580                 585                 590

AAT GGG CAC ATT AAA CTG CCA GGA GTA AGA ACT TAC ATT GAT CCA CAT      1824
Asn Gly His Ile Lys Leu Pro Gly Val Arg Thr Tyr Ile Asp Pro His
        595                 600                 605

ACC TAT GAG GAT CCC AAT CAA GCT GTC CAC GAA TTT GCC AAG GAG ATA      1872
Thr Tyr Glu Asp Pro Asn Gln Ala Val His Glu Phe Ala Lys Glu Ile
    610                 615                 620
```

FIG. 2D

```
GAA GCA TCA TGT ATC ACC ATT GAG AGA GTT ATT GGA GCA GGT GAA TTT      1920
Glu Ala Ser Cys Ile Thr Ile Glu Arg Val Ile Gly Ala Gly Glu Phe
625                 630                 635                 640

GGT GAA GTT TGT AGT GGA CGT TTG AAA CTA CCA GGA AAA AGA GAA TTA      1968
Gly Glu Val Cys Ser Gly Arg Leu Lys Leu Pro Gly Lys Arg Glu Leu
                645                 650                 655

CCT GTG GCT ATC AAA ACC CTT AAA GTA GGC TAT ACT GAA AAG CAA CGC      2016
Pro Val Ala Ile Lys Thr Leu Lys Val Gly Tyr Thr Glu Lys Gln Arg
            660                 665                 670

AGA GAT TTC CTA GGT GAA GCA AGT ATC ATG GGA CAG TTT GAT CAT CCT      2064
Arg Asp Phe Leu Gly Glu Ala Ser Ile Met Gly Gln Phe Asp His Pro
        675                 680                 685

AAC ATC ATC CAT TTA GAA GGT GTG GTG ACC AAA AGT AAA CCA GTG ATG      2112
Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Ser Lys Pro Val Met
    690                 695                 700

ATC GTG ACA GAG TAT ATG GAG AAT GGC TCT TTA GAT ACA TTT TTG AAG      2160
Ile Val Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp Thr Phe Leu Lys
705                 710                 715                 720

AAA AAC GAT GGG CAG TTC ACT GTG ATT CAG CTT GTT GGC ATG CTG AGA      2208
Lys Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met Leu Arg
                725                 730                 735

GGT ATC TCT GCA GGA ATG AAG TAC CTT TCT GAC ATG GGC TAT GTG CAT      2256
Gly Ile Ser Ala Gly Met Lys Tyr Leu Ser Asp Met Gly Tyr Val His
            740                 745                 750

AGA GAT CTT GCT GCC AGA AAC ATC TTA ATC AAC AGT AAC CTT GTG TGC      2304
Arg Asp Leu Ala Ala Arg Asn Ile Leu Ile Asn Ser Asn Leu Val Cys
        755                 760                 765

AAA GTG TCT GAC TTT GGA CTT TCC CGG GTA CTG GAA GAT GAT CCC GAG      2352
Lys Val Ser Asp Phe Gly Leu Ser Arg Val Leu Glu Asp Asp Pro Glu
    770                 775                 780

GCA GCC TAC ACC ACA AGG GGA GGA AAA ATT CCA ATC AGA TGG ACT GCC      2400
Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr Ala
785                 790                 795                 800

CCA GAA GCA ATA GCT TTC CGA AAG TTT ACT TCT GCC AGT GAT GTC TGG      2448
Pro Glu Ala Ile Ala Phe Arg Lys Phe Thr Ser Ala Ser Asp Val Trp
                805                 810                 815

AGT TAT GGA ATA GTA ATG TGG GAA GTT GTG TCT TAT GGA GAG AGA CCC      2496
Ser Tyr Gly Ile Val Met Trp Glu Val Val Ser Tyr Gly Glu Arg Pro
            820                 825                 830
```

FIG. 2E

```
TAC TGG GAG ATG ACC AAT CAA GAT GTG ATT AAA GCG GTA GAG GAA GGC      2544
Tyr Trp Glu Met Thr Asn Gln Asp Val Ile Lys Ala Val Glu Glu Gly
        835                 840                 845

TAT CGT CTG CCA AGC CCC ATG GAT TGT CCT GCT GCT CTC TAT CAG TTA      2592
Tyr Arg Leu Pro Ser Pro Met Asp Cys Pro Ala Ala Leu Tyr Gln Leu
    850                 855                 860

ATG CTG GAT TGC TGG CAG AAA GAG CGA AAT AGC AGG CCC AAG TTT GAT      2640
Met Leu Asp Cys Trp Gln Lys Glu Arg Asn Ser Arg Pro Lys Phe Asp
865                 870                 875                 880

GAA ATA GTC AAC ATG TTG GAC AAG CTG ATA CGT AAC CCA AGT AGT CTG      2688
Glu Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro Ser Ser Leu
                885                 890                 895

AAG ACG CTG GTT AAT GCA TCC TGC AGA GTA TCT AAT TTA TTG GCA GAA      2736
Lys Thr Leu Val Asn Ala Ser Cys Arg Val Ser Asn Leu Leu Ala Glu
            900                 905                 910

CAT AGC CCA CTA GGA TCT GGG GCC TAC AGA TCA GTA GGT GAA TGG CTA      2784
His Ser Pro Leu Gly Ser Gly Ala Tyr Arg Ser Val Gly Glu Trp Leu
        915                 920                 925

GAG GCA ATC AAG ATG GGC CGG TAT ACA GAG ATT TTC ATG GAA AAT GGA      2832
Glu Ala Ile Lys Met Gly Arg Tyr Thr Glu Ile Phe Met Glu Asn Gly
    930                 935                 940

TAC AGT TCA ATG GAC GCT GTG GCT CAG GTG ACC TTG GAG GAT TTG AGA      2880
Tyr Ser Ser Met Asp Ala Val Ala Gln Val Thr Leu Glu Asp Leu Arg
945                 950                 955                 960

CGG CTT GGA GTG ACT CTT GTC GGT CAC CAG AAG AAG ATC ATG AAC AGC      2928
Arg Leu Gly Val Thr Leu Val Gly His Gln Lys Lys Ile Met Asn Ser
                965                 970                 975

CTT CAA GAA ATG AAG GTG CAG CTG GTA AAC GGA ATG GTG CCA TTG TAACTTCATG
2983
Leu Gln Glu Met Lys Val Gln Leu Val Asn Gly Met Val Pro Leu
            980                 985                 990

TAAATGTCGC TTCTTCAAGT GAATGATTCT GCACTTTGTA AACAGCACTG AGATTTATTT    3043

TAACAAAAAA AGGGGGAAAA GGGAAAACAG TGATTTCTAA ACCTTAGAAA ACATTTGCCT    3103

CAGCCACAGA ATTTGTAATC ATGGTTTTAC TGAAGTATCC AGTTCTTAGT CCTTAGTCT     3162
```

FIG. 3A

```
AAGCGGCAGG AGCAGCGTTG GCACCGGCGA ACC ATG GCT GGG ATT TTC TAT TTC        54
                                     Met Ala Gly Ile Phe Tyr Phe
                                       1               5

GCC CTA TTT TCG TGT CTC TTC GGG ATT TGC GAC GCT GTC ACA GGT TCC        102
Ala Leu Phe Ser Cys Leu Phe Gly Ile Cys Asp Ala Val Thr Gly Ser
         10                  15                  20

AGG GTA TAC CCC GCG AAT GAA GTT ACC TTA TTG GAT TCC AGA TCT GTT        150
Arg Val Tyr Pro Ala Asn Glu Val Thr Leu Leu Asp Ser Arg Ser Val
     25                  30                  35

CAG GGA GAA CTT GGG TGG ATA GCA AGC CCT CTG GAA GGA GGG TGG GAG        198
Gln Gly Glu Leu Gly Trp Ile Ala Ser Pro Leu Glu Gly Gly Trp Glu
 40                  45                  50                  55

GAA GTG AGT ATC ATG GAT GAA AAA AAT ACA CCA ATC CGA ACC TAC CAA        246
Glu Val Ser Ile Met Asp Glu Lys Asn Thr Pro Ile Arg Thr Tyr Gln
                60                  65                  70

GTG TGC AAT GTG ATG GAA CCC AGC CAG AAT AAC TGG CTA CGA ACT GAT        294
Val Cys Asn Val Met Glu Pro Ser Gln Asn Asn Trp Leu Arg Thr Asp
             75                  80                  85

TGG ATC ACC CGA GAA GGG GCT CAG AGG GTG TAT ATT GAG ATT AAA TTC        342
Trp Ile Thr Arg Glu Gly Ala Gln Arg Val Tyr Ile Glu Ile Lys Phe
         90                  95                  100

ACC TTG AGG GAC TGC AAT AGT CTT CCG GGC GTC ATG GGG ACT TGC AAG        390
Thr Leu Arg Asp Cys Asn Ser Leu Pro Gly Val Met Gly Thr Cys Lys
    105                 110                 115

GAG ACG TTT AAC CTG TAC TAC TAT GAA TCA GAC AAC GAC AAA GAG CGT        438
Glu Thr Phe Asn Leu Tyr Tyr Tyr Glu Ser Asp Asn Asp Lys Glu Arg
120                 125                 130                 135

TTC ATC AGA GAG AAC CAG TTT GTC AAA ATT GAC ACC ATT GCT GCT GAT        486
Phe Ile Arg Glu Asn Gln Phe Val Lys Ile Asp Thr Ile Ala Ala Asp
                140                 145                 150

GAG AGC TTC ACC CAA GTG GAC ATT GGT GAC AGA ATC ATG AAG CTG AAC        534
Glu Ser Phe Thr Gln Val Asp Ile Gly Asp Arg Ile Met Lys Leu Asn
            155                 160                 165

ACC GAG ATC CGG GAT GTA GGG CCA TTA AGC AAA AAG GGG TTT TAC CTG        582
Thr Glu Ile Arg Asp Val Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu
        170                 175                 180
```

FIG. 3B

```
GCT TTT CAG GAT GTG GGG GCC TGC ATC GCC CTG GTA TCA GTC CGT GTG          630
Ala Phe Gln Asp Val Gly Ala Cys Ile Ala Leu Val Ser Val Arg Val
    185                 190                 195

TTC TAT AAA AAG TGT CCA CTC ACA GTC CGC AAT CTG GCC CAG TTT CCT          678
Phe Tyr Lys Lys Cys Pro Leu Thr Val Arg Asn Leu Ala Gln Phe Pro
200                 205                 210                 215

GAC ACC ATC ACA GGG GCT GAT ACG TCT TCC CTG GTG GAA GTT CGA GGC          726
Asp Thr Ile Thr Gly Ala Asp Thr Ser Ser Leu Val Glu Val Arg Gly
                220                 225                 230

TCC TGT GTC AAC AAC TCA GAA GAG AAA GAT GTG CCA AAA ATG TAC TGT          774
Ser Cys Val Asn Asn Ser Glu Glu Lys Asp Val Pro Lys Met Tyr Cys
            235                 240                 245

GGG GCA GAT GGT GAA TGG CTG GTA CCC ATT GGC AAC TGC CTA TGC AAC          822
Gly Ala Asp Gly Glu Trp Leu Val Pro Ile Gly Asn Cys Leu Cys Asn
        250                 255                 260

GCT GGG CAT GAG GAG CGG AGC GGA GAA TGC CAA GCT TGC AAA ATT GGA          870
Ala Gly His Glu Glu Arg Ser Gly Glu Cys Gln Ala Cys Lys Ile Gly
    265                 270                 275

TAT TAC AAG GCT CTC TCC ACG GAT GCC ACC TGT GCC AAG TGC CCA CCC          918
Tyr Tyr Lys Ala Leu Ser Thr Asp Ala Thr Cys Ala Lys Cys Pro Pro
280                 285                 290                 295

CAC AGC TAC TCT GTC TGG GAA GGA GCC ACC TCG TGC ACC TGT GAC CGA          966
His Ser Tyr Ser Val Trp Glu Gly Ala Thr Ser Cys Thr Cys Asp Arg
                300                 305                 310

GGC TTT TTC AGA GCT GAC AAC GAT GCT GCC TCT ATG CCC TGC ACC CGT         1014
Gly Phe Phe Arg Ala Asp Asn Asp Ala Ala Ser Met Pro Cys Thr Arg
            315                 320                 325

CCA CCA TCT GCT CCC CTG AAC TTG ATT TCA AAT GTC AAC GAG ACA TCT         1062
Pro Pro Ser Ala Pro Leu Asn Leu Ile Ser Asn Val Asn Glu Thr Ser
        330                 335                 340

GTG AAC TTG GAA TGG AGT AGC CCT CAG AAT ACA GGT GGC CGC CAG GAC         1110
Val Asn Leu Glu Trp Ser Ser Pro Gln Asn Thr Gly Gly Arg Gln Asp
    345                 350                 355

ATT TCC TAT AAT GTG GTA TGC AAG AAA TGT GGA GCT GGT GAC CCC AGC         1158
Ile Ser Tyr Asn Val Val Cys Lys Lys Cys Gly Ala Gly Asp Pro Ser
360                 365                 370                 375

AAG TGC CGA CCC TGT GGA AGT GGG GTC CAC TAC ACC CCA CAG CAG AAT         1206
Lys Cys Arg Pro Cys Gly Ser Gly Val His Tyr Thr Pro Gln Gln Asn
                380                 385                 390
```

FIG. 3C

```
GGC TTG AAG ACC ACC AAA GTC TCC ATC ACT GAC CTC CTA GCT CAT ACC      1254
Gly Leu Lys Thr Thr Lys Val Ser Ile Thr Asp Leu Leu Ala His Thr
          395                 400                 405

AAT TAC ACC TTT GAA ATC TGG GCT GTG AAT GGA GTG TCC AAA TAT AAC      1302
Asn Tyr Thr Phe Glu Ile Trp Ala Val Asn Gly Val Ser Lys Tyr Asn
      410                 415                 420

CCT AAC CCA GAC CAA TCA GTT TCT GTC ACT GTG ACC ACC AAC CAA GCA      1350
Pro Asn Pro Asp Gln Ser Val Ser Val Thr Val Thr Thr Asn Gln Ala
  425                 430                 435

GCA CCA TCA TCC ATT GCT TTG GTC CAG GCT AAA GAA GTC ACA AGA TAC      1398
Ala Pro Ser Ser Ile Ala Leu Val Gln Ala Lys Glu Val Thr Arg Tyr
440                 445                 450                 455

AGT GTG GCA CTG GCT TGG CTG GAA CCA GAT CGG CCC AAT GGG GTA ATC      1446
Ser Val Ala Leu Ala Trp Leu Glu Pro Asp Arg Pro Asn Gly Val Ile
              460                 465                 470

CTG GAA TAT GAA GTC AAG TAT TAT GAG AAG GAT CAG AAT GAG CGA AGC      1494
Leu Glu Tyr Glu Val Lys Tyr Tyr Glu Lys Asp Gln Asn Glu Arg Ser
          475                 480                 485

TAT CGT ATA GTT CGG ACA GCT GCC AGG AAC ACA GAT ATC AAA GGC CTG      1542
Tyr Arg Ile Val Arg Thr Ala Ala Arg Asn Thr Asp Ile Lys Gly Leu
      490                 495                 500

AAC CCT CTC ACT TCC TAT GTT TTC CAC GTG CGA GCC AGG ACA GCA GCT      1590
Asn Pro Leu Thr Ser Tyr Val Phe His Val Arg Ala Arg Thr Ala Ala
  505                 510                 515

GGC TAT GGA GAC TTC AGT GAG CCC TTG GAG GTT ACA ACC AAC ACA GTG      1638
Gly Tyr Gly Asp Phe Ser Glu Pro Leu Glu Val Thr Thr Asn Thr Val
520                 525                 530                 535

CCT TCC CGG ATC ATT GGA GAT GGG GCT AAC TCC ACA GTC CTT CTG GTC      1686
Pro Ser Arg Ile Ile Gly Asp Gly Ala Asn Ser Thr Val Leu Leu Val
              540                 545                 550

TCT GTC TCG GGC AGT GTG GTG CTG GTG GTA ATT CTC ATT GCA GCT TTT      1734
Ser Val Ser Gly Ser Val Val Leu Val Val Ile Leu Ile Ala Ala Phe
          555                 560                 565

GTC ATC AGC CGG AGA CGG AGT AAA TAC AGT AAA GCC AAA CAA GAA GCG      1782
Val Ile Ser Arg Arg Arg Ser Lys Tyr Ser Lys Ala Lys Gln Glu Ala
      570                 575                 580

GAT GAA GAG AAA CAT TTG AAT CAA GGT GTA AGA ACA TAT GTG GAC CCC      1830
Asp Glu Glu Lys His Leu Asn Gln Gly Val Arg Thr Tyr Val Asp Pro
  585                 590                 595
```

FIG. 3D

```
TTT ACG TAC GAA GAT CCC AAC CAA GCA GTG CGA GAG TTT GCC AAA GAA      1878
Phe Thr Tyr Glu Asp Pro Asn Gln Ala Val Arg Glu Phe Ala Lys Glu
600                 605                 610                 615

ATT GAC GCA TCC TGC ATT AAG ATT GAA AAA GTT ATA GGA GTT GGT GAA      1926
Ile Asp Ala Ser Cys Ile Lys Ile Glu Lys Val Ile Gly Val Gly Glu
                620                 625                 630

TTT GGT GAG GTA TGC AGT GGG CGT CTC AAA GTG CCT GGC AAG AGA GAG      1974
Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Val Pro Gly Lys Arg Glu
            635                 640                 645

ATC TGT GTG GCT ATC AAG ACT CTG AAA GCT GGT TAT ACA GAC AAA CAG      2022
Ile Cys Val Ala Ile Lys Thr Leu Lys Ala Gly Tyr Thr Asp Lys Gln
        650                 655                 660

AGG AGA GAC TTC CTG AGT GAG GCC AGC ATC ATG GGA CAG TTT GAC CAT      2070
Arg Arg Asp Phe Leu Ser Glu Ala Ser Ile Met Gly Gln Phe Asp His
    665                 670                 675

CCG AAC ATC ATT CAC TTG GAA GGC GTG GTC ACT AAA TGT AAA CCA GTA      2118
Pro Asn Ile Ile His Leu Glu Gly Val Val Thr Lys Cys Lys Pro Val
680                 685                 690                 695

ATG ATC ATA ACA GAG TAC ATG GAG AAT GGC TCC TTG GAT GCA TTC CTC      2166
Met Ile Ile Thr Glu Tyr Met Glu Asn Gly Ser Leu Asp Ala Phe Leu
                700                 705                 710

AGG AAA AAT GAT GGC AGA TTT ACA GTC ATT CAG CTG GTG GGC ATG CTT      2214
Arg Lys Asn Asp Gly Arg Phe Thr Val Ile Gln Leu Val Gly Met Leu
            715                 720                 725

CGT GGC ATT GGG TCT GGG ATG AAG TAT TTA TCT GAT ATG AGC TAT GTG      2262
Arg Gly Ile Gly Ser Gly Met Lys Tyr Leu Ser Asp Met Ser Tyr Val
        730                 735                 740

CAT CGT GAT CTG GCC GCA CGG AAC ATC CTG GTG AAC AGC AAC TTG GTC      2310
His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser Asn Leu Val
    745                 750                 755

TGC AAA GTG TCT GAT TTT GGC ATG TCC CGA GTG CTT GAG GAT GAT CCG      2358
Cys Lys Val Ser Asp Phe Gly Met Ser Arg Val Leu Glu Asp Asp Pro
760                 765                 770                 775

GAA GCA GCT TAC ACC ACC AGG GGT GGC AAG ATT CCT ATC CGG TGG ACT      2406
Glu Ala Ala Tyr Thr Thr Arg Gly Gly Lys Ile Pro Ile Arg Trp Thr
                780                 785                 790

GCG CCA GAA GCA ATT GCC TAT CGT AAA TTC ACA TCA GCA AGT GAT GTA      2454
Ala Pro Glu Ala Ile Ala Tyr Arg Lys Phe Thr Ser Ala Ser Asp Val
            795                 800                 805
```

FIG. 3E

```
TGG AGC TAT GGA ATC GTT ATG TGG GAA GTG ATG TCG TAC GGG GAG AGG      2502
Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met Ser Tyr Gly Glu Arg
        810                 815                 820

CCC TAT TGG GAT ATG TCC AAT CAA GAT GTG ATT AAA GCC ATT GAG GAA      2550
Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile Lys Ala Ile Glu Glu
    825                 830                 835

GGC TAT CGG TTA CCC CCT CCA ATG GAC TGC CCC ATT GCG CTC CAC CAG      2598
Gly Tyr Arg Leu Pro Pro Pro Met Asp Cys Pro Ile Ala Leu His Gln
840                 845                 850                 855

CTG ATG CTA GAC TGC TGG CAG AAG GAG AGG AGC GAC AGG CCT AAA TTT      2646
Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ser Asp Arg Pro Lys Phe
                860                 865                 870

GGG CAG ATT GTC AAC ATG TTG GAC AAA CTC ATC CGC AAC CCC AAC AGC      2694
Gly Gln Ile Val Asn Met Leu Asp Lys Leu Ile Arg Asn Pro Asn Ser
            875                 880                 885

TTG AAG AGG ACA GGG ACG GAG AGC TCC AGA CCT AAC ACT GCC TTG TTG      2742
Leu Lys Arg Thr Gly Thr Glu Ser Ser Arg Pro Asn Thr Ala Leu Leu
        890                 895                 900

GAT CCA AGC TCC CCT GAA TTC TCT GCT GTG GTA TCA GTG GGC GAT TGG      2790
Asp Pro Ser Ser Pro Glu Phe Ser Ala Val Val Ser Val Gly Asp Trp
    905                 910                 915

CTC CAG GCC ATT AAA ATG GAC CGG TAT AAG GAT AAC TTC ACA GCT GCT      2838
Leu Gln Ala Ile Lys Met Asp Arg Tyr Lys Asp Asn Phe Thr Ala Ala
920                 925                 930                 935

GGT TAT ACC ACA CTA GAG GCT GTG GTG CAC GTG AAC CAG GAG GAC CTG      2886
Gly Tyr Thr Thr Leu Glu Ala Val Val His Val Asn Gln Glu Asp Leu
                940                 945                 950

GCA AGA ATT GGT ATC ACA GCC ATC ACG CAC CAG AAT AAG ATT TTG AGC      2934
Ala Arg Ile Gly Ile Thr Ala Ile Thr His Gln Asn Lys Ile Leu Ser
            955                 960                 965

AGT GTC CAG GCA ATG CGA ACC CAA ATG CAG CAG ATG CAC GGC AGA ATG      2982
Ser Val Gln Ala Met Arg Thr Gln Met Gln Gln Met His Gly Arg Met
        970                 975                 980

GTT CCC GTC TGAGCCAGTA CTGAATAAAC TCAAAACTCT TGAAATTAGT              3031
Val Pro Val
    985

TTACCTCATC CATGCACTTT AATTGAAGAA CTGCACTTTT TTTACTTCGT CTTCGCCCTC    3091

TGAAATTAAA GAAATGAAAA AAAAA                                          3116
```

FIG. 4A

```
CGGTGCGAGC GAACAGGAGT GGGGGGGAAA TTAAAAAAAG CTAAACGTGG AGCAGCCGAT      60

CGGGGACCGA GAAGGGGAAT CGATGCAAGG AGCACACTAA AACAAAAGCT ACTTCGGAAC     120

AAACAGCATT TAAAAATCCA CGACTCAAGA TAACTGAAAC CTAAAATAAA ACCTGCTCAT     180

GCACC ATG GTT TTT CAA ACT CGG TAC CCT TCA TGG ATT ATT TTA TGC          227
      Met Val Phe Gln Thr Arg Tyr Pro Ser Trp Ile Ile Leu Cys
        1               5                  10

TAC ATC TGG CTG CTC CGC TTT GCA CAC ACA GGG GAG GCG CAG GCT GCG        275
Tyr Ile Trp Leu Leu Arg Phe Ala His Thr Gly Glu Ala Gln Ala Ala
 15                  20                  25                  30

AAG GAA GTA CTA CTG CTG GAT TCT AAA GCA CAA CAA ACA GAG TTG GAG        323
Lys Glu Val Leu Leu Leu Asp Ser Lys Ala Gln Gln Thr Glu Leu Glu
                35                  40                  45

TGG ATT TCC TCT CCA CCC AAT GGG TGG GAA GAA ATT AGT GGT TTG GAT        371
Trp Ile Ser Ser Pro Pro Asn Gly Trp Glu Glu Ile Ser Gly Leu Asp
            50                  55                  60

GAG AAC TAT ACC CCG ATA CGA ACA TAC CAG GTG TGC CAA GTC ATG GAG        419
Glu Asn Tyr Thr Pro Ile Arg Thr Tyr Gln Val Cys Gln Val Met Glu
         65                  70                  75

CCC AAC CAA AAC AAC TGG CTG CGG ACT AAC TGG ATT TCC AAA GGC AAT        467
Pro Asn Gln Asn Asn Trp Leu Arg Thr Asn Trp Ile Ser Lys Gly Asn
     80                  85                  90

GCA CAA AGG ATT TTT GTA GAA TTG AAA TTC ACC CTG AGG GAT TGT AAC        515
Ala Gln Arg Ile Phe Val Glu Leu Lys Phe Thr Leu Arg Asp Cys Asn
 95                 100                 105                 110

AGT CTT CCT GGA GTA CTG GGA ACT TGC AAG GAA ACA TTT AAT TTG TAC        563
Ser Leu Pro Gly Val Leu Gly Thr Cys Lys Glu Thr Phe Asn Leu Tyr
                115                 120                 125

TAT TAT GAA ACA GAC TAT GAC ACT GGC AGG AAT ATA AGA GAA AAC CTC        611
Tyr Tyr Glu Thr Asp Tyr Asp Thr Gly Arg Asn Ile Arg Glu Asn Leu
            130                 135                 140

TAT GTA AAA ATA GAC ACC ATT GCT GCA GAT GAA AGT TTT ACC CAA GGT        659
Tyr Val Lys Ile Asp Thr Ile Ala Ala Asp Glu Ser Phe Thr Gln Gly
        145                 150                 155

GAC CTT GGT GAA AGA AAG ATG AAG CTT AAC ACT GAG GTG AGA GAG ATT        707
Asp Leu Gly Glu Arg Lys Met Lys Leu Asn Thr Glu Val Arg Glu Ile
    160                 165                 170
```

FIG. 4B

```
GGA CCT TTG TCC AAA AAG GGA TTC TAT CTT GCC TTT CAG GAT GTA GGG      755
Gly Pro Leu Ser Lys Lys Gly Phe Tyr Leu Ala Phe Gln Asp Val Gly
175                 180                 185                 190

GCT TGC ATA GCT TTG GTT TCT GTC AAA GTG TAC TAC AAG AAG TGC TGG      803
Ala Cys Ile Ala Leu Val Ser Val Lys Val Tyr Tyr Lys Lys Cys Trp
                195                 200                 205

TCC ATT ATT GAG AAC TTA GCT ATC TTT CCA GAT ACA GTG ACT GGT TCA      851
Ser Ile Ile Glu Asn Leu Ala Ile Phe Pro Asp Thr Val Thr Gly Ser
            210                 215                 220

GAA TTT TCC TCT TTA GTC GAG GTT CGA GGG ACA TGT GTC AGC AGT GCA      899
Glu Phe Ser Ser Leu Val Glu Val Arg Gly Thr Cys Val Ser Ser Ala
        225                 230                 235

GAG GAA GAA GCG GAA AAC GCC CCC AGG ATG CAC TGC AGT GCA GAA GGA      947
Glu Glu Glu Ala Glu Asn Ala Pro Arg Met His Cys Ser Ala Glu Gly
    240                 245                 250

GAA TGG TTA GTG CCC ATT GGA AAA TGT ATC TGC AAA GCA GGC TAC CAG      995
Glu Trp Leu Val Pro Ile Gly Lys Cys Ile Cys Lys Ala Gly Tyr Gln
255                 260                 265                 270

CAA AAA GGA GAC ACT TGT GAA CCC TGT GGC CGT GGG TTC TAC AAG TCT     1043
Gln Lys Gly Asp Thr Cys Glu Pro Cys Gly Arg Gly Phe Tyr Lys Ser
                275                 280                 285

TCC TCT CAA GAT CTT CAG TGC TCT CGT TGT CCA ACT CAC AGT TTT TCT     1091
Ser Ser Gln Asp Leu Gln Cys Ser Arg Cys Pro Thr His Ser Phe Ser
            290                 295                 300

GAT AAA GAA GGC TCC TCC AGA TGT GAA TGT GAA GAT GGG TAT TAC AGG     1139
Asp Lys Glu Gly Ser Ser Arg Cys Glu Cys Glu Asp Gly Tyr Tyr Arg
        305                 310                 315

GCT CCA TCT GAC CCA CCA TAC GTT GCA TGC ACA AGG CCT CCA TCT GCA     1187
Ala Pro Ser Asp Pro Pro Tyr Val Ala Cys Thr Arg Pro Pro Ser Ala
    320                 325                 330

CCA CAG AAC CTC ATT TTC AAC ATC AAC CAA ACC ACA GTA AGT TTG GAA     1235
Pro Gln Asn Leu Ile Phe Asn Ile Asn Gln Thr Thr Val Ser Leu Glu
335                 340                 345                 350

TGG AGT CCT CCT GCA GAC AAT GGG GGA AGA AAC GAT GTG ACC TAC AGA     1283
Trp Ser Pro Pro Ala Asp Asn Gly Gly Arg Asn Asp Val Thr Tyr Arg
                355                 360                 365

ATA TTG TGT AAG CGG TGC AGT TGG GAG CAG GGC GAA TGT GTT CCC TGT     1331
Ile Leu Cys Lys Arg Cys Ser Trp Glu Gln Gly Glu Cys Val Pro Cys
            370                 375                 380
```

FIG. 4C

```
GGG AGT AAC ATT GGA TAC ATG CCC CAG CAG ACT GGA TTA GAG GAT AAC      1379
Gly Ser Asn Ile Gly Tyr Met Pro Gln Gln Thr Gly Leu Glu Asp Asn
        385                 390                 395

TAT GTC ACT GTC ATG GAC CTG CTA GCC CAC GCT AAT TAT ACT TTT GAA      1427
Tyr Val Thr Val Met Asp Leu Leu Ala His Ala Asn Tyr Thr Phe Glu
    400                 405                 410

GTT GAA GCT GTA AAT GGA GTT TCT GAC TTA AGC CGA TCC CAG AGG CTC      1475
Val Glu Ala Val Asn Gly Val Ser Asp Leu Ser Arg Ser Gln Arg Leu
415                 420                 425                 430

TTT GCT GCT GTC AGT ATC ACC ACT GGT CAA GCA GCT CCC TCG CAA GTG      1523
Phe Ala Ala Val Ser Ile Thr Thr Gly Gln Ala Ala Pro Ser Gln Val
                435                 440                 445

AGC GGA GTA ATG AAG GAG AGA GTA CTG CAG CGG AGT GTC GAG CTT TCC      1571
Ser Gly Val Met Lys Glu Arg Val Leu Gln Arg Ser Val Glu Leu Ser
            450                 455                 460

TGG CAG GAA CCA GAG CAT CCC AAT GGA GTC ATC ACA GAA TAT GAA ATC      1619
Trp Gln Glu Pro Glu His Pro Asn Gly Val Ile Thr Glu Tyr Glu Ile
        465                 470                 475

AAG TAT TAC GAG AAA GAT CAA AGG GAA CGG ACC TAC TCA ACA GTA AAA      1667
Lys Tyr Tyr Glu Lys Asp Gln Arg Glu Arg Thr Tyr Ser Thr Val Lys
    480                 485                 490

ACC AAG TCT ACT TCA GCC TCC ATT AAT AAT CTG AAA CCA GGA ACA GTG      1715
Thr Lys Ser Thr Ser Ala Ser Ile Asn Asn Leu Lys Pro Gly Thr Val
495                 500                 505                 510

TAT GTT TTC CAG ATT CGG GCT TTT ACT GCT GCT GGT TAT GGA AAT TAC      1763
Tyr Val Phe Gln Ile Arg Ala Phe Thr Ala Ala Gly Tyr Gly Asn Tyr
                515                 520                 525

AGT CCC AGA CTT GAT GTT GCT ACA CTA GAG GAA GCT ACA GGT AAA ATG      1811
Ser Pro Arg Leu Asp Val Ala Thr Leu Glu Glu Ala Thr Gly Lys Met
            530                 535                 540

TTT GAA GCT ACA GCT GTC TCC AGT GAA CAG AAT CCT GTT ATT ATC ATT      1859
Phe Glu Ala Thr Ala Val Ser Ser Glu Gln Asn Pro Val Ile Ile Ile
        545                 550                 555

GCT GTG GTT GCT GTA GCT GGG ACC ATC ATT TTG GTG TTC ATG GTC TTT      1907
Ala Val Val Ala Val Ala Gly Thr Ile Ile Leu Val Phe Met Val Phe
    560                 565                 570

GGC TTC ATC ATT GGG AGA AGG CAC TGT GGT TAT AGC AAA GCT GAC CAA      1955
Gly Phe Ile Ile Gly Arg Arg His Cys Gly Tyr Ser Lys Ala Asp Gln
575                 580                 585                 590
```

FIG. 4D

```
GAA GGC GAT GAA GAG CTT TAC TTT CAT TTT AAA TTT CCA GGC ACC AAA      2003
Glu Gly Asp Glu Glu Leu Tyr Phe His Phe Lys Phe Pro Gly Thr Lys
                595                 600                 605

ACC TAC ATT GAC CCT GAA ACC TAT GAG GAC CCA AAT AGA GCT GTC CAT      2051
Thr Tyr Ile Asp Pro Glu Thr Tyr Glu Asp Pro Asn Arg Ala Val His
            610                 615                 620

CAA TTC GCC AAG GAG CTA GAT GCC TCC TGT ATT AAA ATT GAG CGT GTG      2099
Gln Phe Ala Lys Glu Leu Asp Ala Ser Cys Ile Lys Ile Glu Arg Val
        625                 630                 635

ATT GGT GCA GGA GAA TTC GGT GAA GTC TGC AGT GGC CGT TTG AAA CTT      2147
Ile Gly Ala Gly Glu Phe Gly Glu Val Cys Ser Gly Arg Leu Lys Leu
    640                 645                 650

CCA GGG AAA AGA GAT GTT GCA GTA GCC ATA AAA ACC CTG AAA GTT GGT      2195
Pro Gly Lys Arg Asp Val Ala Val Ala Ile Lys Thr Leu Lys Val Gly
655                 660                 665                 670

TAC ACA GAA AAA CAA AGG AGA GAC TTT TTG TGT GAA GCA AGC ATC ATG      2243
Tyr Thr Glu Lys Gln Arg Arg Asp Phe Leu Cys Glu Ala Ser Ile Met
                675                 680                 685

GGG CAG TTT GAC CAC CCA AAT GTT GTC CAT TTG GAA GGG GTT GTT ACA      2291
Gly Gln Phe Asp His Pro Asn Val Val His Leu Glu Gly Val Val Thr
            690                 695                 700

AGA GGG AAA CCA GTC ATG ATA GTA ATA GAG TTC ATG GAA AAT GGA GCC      2339
Arg Gly Lys Pro Val Met Ile Val Ile Glu Phe Met Glu Asn Gly Ala
        705                 710                 715

CTA GAT GCA TTT CTC AGG AAA CAT GAT GGG CAA TTT ACA GTC ATT CAG      2387
Leu Asp Ala Phe Leu Arg Lys His Asp Gly Gln Phe Thr Val Ile Gln
    720                 725                 730

TTA GTA GGA ATG CTG AGA GGA ATT GCT GCT GGA ATG AGA TAT TTG GCT      2435
Leu Val Gly Met Leu Arg Gly Ile Ala Ala Gly Met Arg Tyr Leu Ala
735                 740                 745                 750

GAT ATG GGA TAT GTT CAC AGG GAC CTT GCA GCT CGC AAT ATT CTT GTC      2483
Asp Met Gly Tyr Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val
                755                 760                 765

AAC AGC AAT CTC GTT TGT AAA GTG TCA GAT TTT GGC CTG TCC CGA GTT      2531
Asn Ser Asn Leu Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Val
            770                 775                 780

ATA GAG GAT GAT CCA GAA GCT GTC TAT ACA ACT ACT GGT GGA AAA ATT      2579
Ile Glu Asp Asp Pro Glu Ala Val Tyr Thr Thr Thr Gly Gly Lys Ile
        785                 790                 795
```

FIG. 4E

```
CCA GTA AGG TGG ACA GCA CCC GAA GCC ATC CAG TAC CGG AAA TTC ACA      2627
Pro Val Arg Trp Thr Ala Pro Glu Ala Ile Gln Tyr Arg Lys Phe Thr
    800                 805                 810

TCA GCC AGT GAT GTA TGG AGC TAT GGA ATA GTC ATG TGG GAA GTT ATG      2675
Ser Ala Ser Asp Val Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met
815                 820                 825                 830

TCT TAT GGA GAA AGA CCT TAT TGG GAC ATG TCA AAT CAA GAT GTT ATA      2723
Ser Tyr Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile
                835                 840                 845

AAA GCA ATA GAA GAA GGT TAT CGT TTA CCA GCA CCC ATG GAC TGC CCA      2771
Lys Ala Ile Glu Glu Gly Tyr Arg Leu Pro Ala Pro Met Asp Cys Pro
        850                 855                 860

GCT GGC CTT CAC CAG CTA ATG TTG GAT TGT TGG CAA AAG GAG CGT GCT      2819
Ala Gly Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Glu Arg Ala
    865                 870                 875

GAA AGG CCA AAA TTT GAA CAG ATA GTT GGA ATT CTA GAC AAA ATG ATT      2867
Glu Arg Pro Lys Phe Glu Gln Ile Val Gly Ile Leu Asp Lys Met Ile
880                 885                 890

CGA AAC CCA AAT AGT CTG AAA ACT CCC CTG GGA ACT TGT AGT AGG CCA      2915
Arg Asn Pro Asn Ser Leu Lys Thr Pro Leu Gly Thr Cys Ser Arg Pro
895                 900                 905                 910

ATA AGC CCT CTT CTG GAT CAA AAC ACT CCT GAT TTC ACT ACC TTT TGT      2963
Ile Ser Pro Leu Leu Asp Gln Asn Thr Pro Asp Phe Thr Thr Phe Cys
                915                 920                 925

TCA GTT GGA GAA TGG CTA CAA GCT ATT AAG ATG GAA AGA TAT AAA GAT      3011
Ser Val Gly Glu Trp Leu Gln Ala Ile Lys Met Glu Arg Tyr Lys Asp
        930                 935                 940

AAT TTC ACG GCA GCT GGC TAC AAT TCC CTT GAA TCA GTA GCC AGG ATG      3059
Asn Phe Thr Ala Ala Gly Tyr Asn Ser Leu Glu Ser Val Ala Arg Met
    945                 950                 955

ACT ATT GAG GAT GTG ATG AGT TTA GGG ATC ACA CTG GTT GGT CAT CAA      3107
Thr Ile Glu Asp Val Met Ser Leu Gly Ile Thr Leu Val Gly His Gln
960                 965                 970

AAG AAA ATC ATG AGC AGC ATT CAG ACT ATG AGA GCA CAA ATG CTA CAT      3155
Lys Lys Ile Met Ser Ser Ile Gln Thr Met Arg Ala Gln Met Leu His
975                 980                 985                 990

TTA CAT GGA ACT GGC ATT CAA GTG TGATATGCAT TTCTCCCTTT TAAGGGAGAT     3209
Leu His Gly Thr Gly Ile Gln Val
                995
```

FIG. 4F

TACAGACTGC AAGAGAACAG TACTGGCCTT CAGTATATGC ATAGAATGCT GCTAGAAGAC 3269

AAGTGATGTC CTGGGTCCTT CCAACAGTGA AGAGAAGATT TAAGAAGCAC CTATAGACTT 3329

GAACTCCTAA GTGCCACCAG AATATATAAA AAGGGAATTT AGGATCCACC ATCGGTGGCC 3389

AGGAAAATAG CAGTGACAAT AAACAAAGTA CTACCTGAAA AACATCCAAA CACCTTGAGC 3449

TCTCTAACCT CCTTTTTGTC TTATAGACTT TTTAAAATGT ACATAAAGAA TTTAAGAAAG 3509

AATATATTTG TCAAATAAAA TCATGATCTT ATTGTTAAAA TTAATGAAAT ATTTTCCTTA 3569

AATATGTGAT TTCAGACTAT TCCTTTTTAA AATCATTTGT GTTTATTCTT CATAAGGACT 3629

TTGTTTTAGA AAGCTGTTTA TAGCTTTGGA CCTTTTTAGT GTTAAATCTG TAACATTACT 3689

ACACTGGGTA CCTTTGAAAG AATCTCAAAT TTCAAAAGAA ATAGCATGAT TGAAGATACA 3749

TCTCTGTTAG AACATTGGTA TCCTTTTTGT GCCATTTTAT TCTGTTTAAT CAGTGCTGTT 3809

TTGATATTGT TTGCTAATTG GCAGGTAGTC AAGAAAATGC AAGTTGCCAA GAGCTCTGAT 3869

ATTTTTTAAA AAGAATTTTT TTGTAAAGAT CAGACAACAC ACTATCTTTT CAATGAAAAA 3929

AGCAATAATG ATCCATACAT ACTATAAGGC ACTTTTAACA GATTGTTTAT AGAGTGATTT 3989

TACTAGAAAG AATTTAATAA ACTCGAAGTT TAGGTTTATG AGTATATAAA CAAATGAGGC 4049

ACTTCATCTG AAGAATGTTG GTGAAGGCAA GTCTCTGAAA GCAGAACTAT CCAGTGTTAT 4109

CTAAAAATTA ATCTGAGCAC ATCAAGATTT TTTCATTCTC GTGACATTAG GAAATTTAGG 4169

ATAAATAGTT GACATATATT TTATATCCTC TTCTGTTGAA TGCAGTCCAA ACATGAAAGG 4229

AAATAATTGT TTTATATTAT AACTCTGAAG CATGATAAAG GGGCAGTTCA CAATTTTCAC 4289

CATTTAAACA CAAATTTGCT GCACAGAATA TCACCATTGC AGTTCAAAAC AAAACAAAAC 4349

AAAAAGTCTT TTGTTTGTGA ACACTGATGC AAGAAACTTG TTAAATGAAA GGACTCTTTA 4409

CCCTAGAAGG AAGAGGTGAA GGATCTGGCT TGTTTTTAAA GCTTTATTTA TTAAACCATA 4469

TTATTTGATT ACTGTGTTAG AATTTCATAA GCAATAATTA AATGTGTCTT TATGGAATTC 4529

FIG. 5A

```
                                                                                                                    *
CONS   MARARPP........s..ll..llllldal...aa.pa.EvtLlDskt.qgeLgWishPp..GWee.sg.den.tpirtYqvCnvme.sqnn.WLrtnwi:
EPH                 MERRWPLGLGLVLLLCAPLPPGARAKEVTLMDTSKAQGELGWLLDPPKDGWSEQQQILNGT.PLYMYQDCPMQGRRDTDHWLRSNWIY
ECK                MELQAARACFALLWGCALAAAAAAAQGKEVVLLDFAAAGGELGWLTHPYGKGWDLMQNIMNDM.PIYMYSVCNVMSGDQDN.WLRTNWVY
HEK4              MDCQLSILLLLLSCSVLDSFGELIPQPSNEVNLLDSKTIQGELGWISYPSH.GWEEISGVDEHYTPIRTYQVCNVMDHSQNN.WLRTNWVP
HEK5                                      LLAAVEETLMDSTTATAELGWMVHPPS.GWEEVSGYDENMNTIRTYQVCNVFESSQNN.WLRTKFIR
HEK7                                   ALRTLLASPSNEVNLLDSRTVMGDLGWIAFPKN.GWEEIGEVDENYAPIHTYQVCKVMEQNQNN.WLLTSWIS
HEK8             MAGIFYFALFSCLFGICDAVTGSRVYPANEVTLLDSRSVQGELGWIASPLEGGWEEVSIMDEKNTPIRTYQVCNVMEPSQNN.WLRTDWIT
HEK2   MARARPPPPPSPPPGLLPLLPPLLLLPLLLLPAGCRALEETLMDTKWVTSELAWTSHPES.GWEEVSGYDEAMNPIRTYQVCNVRESSQNN.WLRTGFIW
HEK11           MVFQTRYPSWIILCYIWLLRFAHTGEAQAAKEVLLLDSKAQQTELEWISSPPN.GWEEISGLDENYTPIRTYQVCQVMEPNQNN.WLRTNWIS
                                  *                 *

CONS   rg.gaqriyvElkFt.RDCnS.Pgvlgt..CKETFNlyYyEsDdd....tgrniren.fvKidTiAaDesftq.Dlgdr.mklNtevrsvGplskkGfYL
EPH    RGEEASRVHVELQFTVRDCKSFPGGAGPLGCKETFNLLYMESDQD....VGIQLRRPLFQKVTTVAADQSFTIRDLASGSVKLNVERCSLGRLTRRGLYL
ECK    RG.EAERNNFELNFTVRDCNSFPGGASS..CKETFNLYYAESDLD....YGTNFQKRLFTKIDTIAPDEITVSSDFEARHVKLNVEERSVGPLTRKGFYL
HEK4   RN.SAQKIYVELKFTLRDCNSIPLVLGT..CKETFNLYYMESDDD....HGVKFREHQFTKIDTIAADESFTQMDLGDRILKLNTEIREVGPVNKKGFYL
HEK5   RR.GAHRIHVEMKFSVRDCSSIPSVPGS..CKETFNLYYYEADFDSATKTFPNWMENPWVKVDTIAADESFSQVDLGGRVMKINTEVRSFGPVSRSGFYL
HEK7   NE.GASRIFIELKFTLRDCNSLPGGLGT..CKETFNMYYFESDDQ....NGRNIKENQYIKIDTIAADESFTELDLGDRVMKLNTEVRDVGPLSKKGFYL
HEK8   RE.GAQRVYIEIKFTLRDCNSLPGVMGT..CKETFNLYYYESDND....KERFIRENQFVKIDTIAADESFTQVDIGDRIMKLNTEIRDVGPLSKKGFYL
HEK2   RR.DVQRVYVELKFTVRDCNSIPNIPGS..CKETFNLFYYEADSDVASASSPFWMENPYVKVDTIAPDESFSRLDAGRV....NTKVRSFGPLSKAGFYL
HEK11  KG.NAQRIFVELKFTLRDCNSLPGVLGT..CKETFNLYYYETDYD....TGRNIRENLYVKIDTIAADESFTQGDLGERKMKLNTEVREIGPLSQKGFYL
```

FIG. 5B

```
              *            *                            *                 *            * *            *  *
CONS   AFqdvGaC.aLvsVrv.ykkCpstv.nlA.FpdT.tgadsssLvevrG.Cvnna....e...pp.m.CsadGEWlVPiGkC.CkaGyee...gtaCqaCp
EPH    AFHNPGACVALVSVRVFYQRCPETLNGLAQFPDTLPG.PA.GLVEVAGTCLPHARASPRPSGAPRMHCSPDGEWLVPVGRCHCEPGYEEGGSGEACVACP
ECK    AFQDIGACVALLSVRVYYKKCPELLQGLAHFPETIAGSDAPSLATVAGTCVDHA.VVPPGGEEPRMHCAVDGEWLVPIGQCLCQAGYEKVED..ACQACS
HEK4   AFQDVGACVALVSVRVYFKKCPFTVKNLAMFPDTVP.MDSQSLVEVRGSCVNNS....KEEDPPRMYCSTEGEWLVPIGKCSCNAGYEER..GFMCQACR
HEK5   AFQDYGGCMSLIAVRVFYRKCPRIIQNGAIFQETLSGAESTSLVAARGSCIANA...EEVDVPIKLYCNGDGEWLVPIGRCMCKAGFEAVENGTVCRGCP
HEK7   AFQDVGACIALVSVRVYYKKCPSVVRHLAVFPDTITGADSSQLLEVSGSCVNHS....VTDEPPKMHCSAEGEWLVPIGKCMCKAGYEEK.NGT.CQVCR
HEK8   AFQDVGACIALVSVRVFYKKCPLTVRNLAQFPDTITGADTSSLVEVRGSCVNNS....EEKDVPKMYCGADGEWLVPIGNCLCNAGHEER..SGECQACK
HEK2   AFQDQGACMSLISVRAFYKKCASTTAGFALFPETLTGAEPTSLVIAPGTCIPNA...VEVSVPLKLYCNGDGEWMVPVGACTCATGHEPAAKESQCRPCP
HEK11  AFQDVGACIALVSVKVYYKKCWSIIENLAIFPDTVTGSEFSSLVEVRGTCVSSA..EEEAENAPRMHCSAEGEWLVPIGKCICKAGYQQK..GDTCEPCG
                   *  *             * *               *                                        *  *
CONS   pGfyka..gd.pClkCPphs.ttsegatsCtCengy.RadsdppsmaCTrpPSaPrnlisnvnetsv.LeWspPadtGgR.Dv.yn.iCkkCg.ga...g
EPH    SGSYRMDMDTPHCLTCPQQSTAESEGATICTCESGHYRAPGEGPQVACTGPPSAPRNLSFSASGTQLSLRWEPPADTGGRQDVRYSVRCSQCQGTAQDGG
ECK    PGFFKFEASESPCLECPEHTLPSPEGATSCECEEGFFRAPQDPASMPCTRPPSAPHYLTAVGMGAKVELRWTPPQDSGGREDIVYSVTCEQCWPES...G
HEK4   PGFYKALDGNMKCAKCPPHSSTQEDGSMNCRCENNYFRADKDPPSMACTRPPSSPRNVISNINETSVILDWSWPLDTGGRKDVTFNIICKKCGWNI...K
HEK5   SGTFKANQGDEACTHCPINSRTTSEGATNCVCRNGYYRADLDPLDMPCTTIPSAPQAVISSVNETSLMLEWTPPRDSGGREDLVYNIICKSCGSGR...G
HEK7   PGFFKASPHIQSCGKCPPHSYTHEEASTSCVCEKDYFRRESDPPTMACTRPPSAPRNAISNVNETSVFLEWIPPADTGGRKDVSYYIACKKCNSHA...G
HEK8   IGYYKALSTDATCAKCPPHSYSVWEGATSCTCDRGFFRADNDAASMPCTRPPSAPLNLISNVNETSVNLEWSSPQNTGGRQDISYNVVCKKCGAGD..PS
HEK2   PGSYKAKQGEGPCLPCPPNSRTTSPAASICTCHNNFYRADSDSADSACTTVPSPPRGVISNVNETSLILEWSEPRDLGVRDDLLYNVICKKC.HGAGGAS
HEK11  RGFYKSSSQDLQCSRCPTHSFSDKEGSSRCECEDGYYRAPSDPPYVACTRPPSAPQNLIFNINQTTVSLEWSPPADNGGRNDVTYRILCKRCSWEQ...G
```

FIG. 5C

```
          *  *
CONS   .CepCg.nvry.prqlgLt.t.vtvsdLlahtnYtFe.eAvNGVs.l....sp.q.asvsv.ittnqaaps.v.tvr....sr.s.slsW.qep.rpngv
EPH    PCQPCGVGVHFSPGARALTTPAVHVNGLEPYANYTFNVEAQNGVSGLGSSGHAS..TSVSISMGHAESLS..GLSLRLVKKEPRQLELTWAGSRPRSPGA
ECK    ECGPCEASVRYSEPPHGLTRTSVTVSDLEPHMNYTFTVEARNGVSGLVTSRSFR.TASVS..I..NQ...TEPPKVRLEGRSTTSLSVSW.SIPPPQQSR
HEK4   QCEPCSPNVRFLPRQFGLTNTTVTVTDLLAHTNYTFEIDAVNGVSEL..SSPPRQFAAV..SITTNQAAPSPVLTIKKDRTSRNSISLSW.QEPEHPNGI
HEK5   ACTRCGDNVQYAPRQLGLTEPRIYISDLLAHTQYTFEIQAVNGVTD..QSPFSPQFASV..NITTNQAAPSAVSIMHQVSRTVDSITLSW.SQPDQPNGV
HEK7   VCEECGGHVRYLPRQSGLKNTSVMMVDLLAHTNYTFEIEAVNGVSDL....SPGARQYVSVNVTTNQAAPSPVTNVKKGKIAKNSISLSW.QEPDRPNGI
HEK8   KCRPCGSGVHYTPQQNGLKTTKVSITDLLAHTNYTFEIWAVNGVSK....YNPNPDQSVSVTVTTNQAAPSSIALVQAKEVTRYSVALAW.LEPDRPNGV
HEK2   ACSRCDDNVEFVPRQLGLSEPRVHTSHLLAHTRYTFEVQAVNGVSGK....SPLPPRYAAVNITTNQAAPSEVPTLRLHSSSGSSLTLSW.APPERPNGV
HEK11  ECVPCGSNIGYMPQQTGLEDNYVTVMDLLAHANYTFEVEAVNGVSDL....SRSQRLFAAVSITTGQAAPSQVSGVMKERVLQRSVELSW.QEPEHPNGV

CONS   il.YEvkyyekdq.ersy.iv..k.tsvt.dgLkpdt.YvfqvrarTaaGyG..Sr..efeT.pea.sgsg...ivvviivs.aga..llvv..v.l..r
EPH    NLTYE....LHVLNQDEERYQMVLEPRVLLTELQPDTTYIVRVRMLTPLGPGPFSPDHEFRTSPPVSRGLTGGEIVAVIFGLLLGAALLLGILVFRSRRA
ECK    VWKYEV.TYRKKGDSNSYNVRRTEGFSVTLDDLAPDTTYLVQVQALTQEGQGAGSKVHEFQTLSPEGSGNLAVIGGVAVGVVLLLVLAGVGFFIHRRRKN
HEK4   ILDYEVKYYEKQEQETSYTILRARGTNVTISSLKPDTIYVLQIRARTAAGYGTNSRKFEFETSPDSFSISGESSQVVMIAISAAVAIILLTVVIYVLIGR
HEK5   ILDYELQYYEKELSEYNATAIKSPTNTVTVQGLKAGAIYVFQVRARTVAGYGRYSGKMYFQTMTEAEYQTSIQEKLPLIIGSSAAGLVFLIAVVVIAIVC
HEK7   ILEYEIKHFEKDQETSYTII.KSKETTITAEGLKPASVYVFQIRARTAAGYGVFSRRFEFETTPVFAASSDQSQIPVIAVSVTVGVILLAVVIGVLLSGR
HEK8   ILEYEVKYYEKDQNERSYRIVRTAARNTDIKGLNPLTSYVFHVRARTAAGYGDFSEPLEVTTNTVPSRIIGDGANSTVLLVSVSGSVVLVVILIAAFVIS
HEK2   ILDYEMKYFEK..SEGIASTVTSQMNSVQLDGLRPDARYVVQVRARTVAGYGQYSRPAEFETTSERGSGAQQLQEQLPLIVGSATAGLVFVVAVVVIAIV
HEK11  ITEYEIKYYEKDQRERTYSTVKTKSTSASINNLKPGTVYVFQIRAFTAAGYGNYSPRLDVATLEEATGKMFEATAVSSEQNPVIIIAVVXVAGTIILVFM
```

SUBSTITUTE SHEET (RULE 26)

FIG. 5D


```
CONS   .r..qsr.dd.ey.keq.....klpg.ktyidP.TyedPnqav.efakEidascikiekViGaGEFGEVcsGrLklp.gkre..VAIKTLKvgy
EPH    QRQRQQRHVTAPPMWIERTSCAEALCGTSRHTRTLHREPWTL..PGGWSNFPSRELDPAWLMVDTVIGEGEFGEVYRGTLRLPS.QDCKTVAIKTLKDTS
ECK    QRARQSPEDVYFSKSEQ.....LKPLKTYVDPHTYEDPNQAVLKFTTEIHPSCVTRQKVIGAGEFGEVYKGMLKTSSGKKEVPVAIKTLKAGY
HEK4   FCGYKSKHGADEKRLHFGNG.....HLKLPGLRTYVDPHTYEDPTQAVHEFAKELDATNISIDKVVGAGEFGEVCSGRLKLPS.KKEISVAIKTLKVGY
HEK5   NRRGFERADSEYTDKLQHYT.....SGHITPGMKIYIDPFTYEDPNEAVREFAKEIDISCVKIEQVIGAGEFGEVCSGHLKLP.GKREIFVAIKTLKSGY
HEK7   RCGYSKAKQDPEEEKMHFHN.....GHIKLPGVRTYIDPHTYEDPNQAVHEFAKEIEASCITIERVIGAGEFGEVCSGRLKLP.GKRELPVAIKTLKVGY
HEK8   RRRSKYSKAKQEADEEKHLN.....QGVRTYVDPFTYEDPNQAVREFAKEIDASCIKIEKVIGVGEFGEVCSGRLKVP.GKREICVAIKTLKAGY
HEK2   CLRKQRHGSDSEYTEKLQQY.....IAPGMKVYIDPFTYEDPNEAVREFAKEIDVSCVKIEEVIGAGEFGEVCRGRLKQP.GRREVFVAIKTLKVGY
HEK11  VFGFIIGRRHCGYTKADQEGDEELYFHFKFPGTKTYIDPETYEDPNRAVHQFAKELDASCIKIERVIGAGEFGEVCSGRLKLP.GKRDVAVAIKTLKVGY

CONS   tekQrrdFL.EAsIMGQFdHpniihLEGVvtkskPvMIitE.MENg.Ld.FLrkndgqftviQLVgMLrGIaaGMkYLsdmnYVHRDLAARNILvNsNLv
EPH    PGGQWWNFLREATIMGQFSHPHILHLEGVVTKRKPIMIITEFMENAALDAFLRREREDQLVPGQLVAMLQGIASGMNYLSNHNYVHRDLAARNILVNQNLC
ECK    TEKQRVDFLGEAGIMGQFSHHNIIRLEGVISKYKPMMIITEYMENGALDKFLREKDGEFSVLQLVGMLRGIAAGMKYLANMNYVHRDLAARNILVNSNLV
HEK4   TEKQRRDFLGEASIMGQFDHPNIIRLEGVVTKSKPVMIVTEYMENGSLDSFLRKHDAQFTVIQLVGMLRGIASGMKYLSDMGYVHRDLAARNILINSNLV
HEK5   TEKQRRDFLSEASIMGQFDHPNVIHLEGVVTKSTPVMIITEFMENGSLDSFLRQNDGQFTVIQLVGMLRGIAAGMKYLADMNYVHRDLAARNILVNSNLV
HEK7   TEKQRRDFLGEASIMGQFDHPNIIHLEGVVTKSKPVMIVTEYMENGSLDTFLKKNDGQFTVIQLVGMLRGISAGMKYLSDMGYVHRDLAARNILINSNLV
HEK8   TDKQRRDFLSEASIMGQFDHPNIIHLEGVVTKCKPVMIITEYMENGSLDAFLRKNDGRFTVIQLVGMLRGIGSGMKYLSDMSYVHRDLAARNILVNSNLV
HEK2   TERQRRDFLSEASIMGQFDHPNIIRLEGVVTKSRPVMILTEFMENCALDSFLRLNDGQFTVIQLVGMLRGIAAGMKYLSEMNYVHRDLAARNILVNSNLV
HEK11  TEKQRRDFLCEASIMGQFDHPNVVHLEGVVTRGKPVMIVIEFMENGALHAFLRKHDGQFTVIQLVGMLRGIAAGMRYLADMGYVHRDLAARNILVNSNLV
```

FIG. 5E

```
      *                                                                                             *
CONS  CKVSDFGlsRvleDD.pea.yT.trGGkiPiRWTaPEAIayRkFTsASDVWSyGIVmWEVmsyGerPYw.msNqdVikaieegyRLPpPmDCPaal.qLM
EPH   CKVSDFGLTRLL.DDFDGTYET..QGGKIPIRWTAPEAIAHRIFTTASDVWSFGIVMWEVLSFGDKPYGEMSNQEVMKSIEDGYRLPPPVDCPAPLYELM
ECK   CKVSDFGLSRVLEDD.PEATYT.TSGGKIPIRWTAPEAISYRKFTSASDVWSFGIVMWEVMTYGERPYWELSNHEVMKAINDGFRLPTPMDCPSAIYQLM
HEK4  CKVSDFGLSRVLEDD.PEAAYT.TRGGKIPIRWTSPEAIAYRKFTSASDVWSYGIVLWEVMSYGERPYWEMSNQDVIKAVDEGYRLPPPMDCPAALYQLM
HEK5  CKVSDFGLSRFLEDDTSDPTYTSALGGKFPIRWTAPEAIQYRKFTSASDVWSYGIVMWEVMSYGERPYWDMTNQDVINAIEQDYRLPPPMDCPSALHQLM
HEK7  CKVSDFGLSRVLEDD.PEAAYT.TRGGKIPIRWTAPEAIAFRKFTSASDVWSYGIVMWEVVSYGERPYWEMTNQDVIKAVEEGYRLPSPMDCPAALYQLM
HEK8  CKVSDFGMSRVLEDD.PEAAYT.TRGGKIPIRWTAPEAIAYRKFTSASDVWSYGIVMWEVMSYGERPYWDMSNQDVIKAIEEGYRLPPPMDCPIALHQLM
HEK2  CKVSDFGLSRFLEDDPSDPTYTSSLGGKIPIRWTAPEAIAYRKFTSASDVWSYGIVMWEVMSYGERPYWDMSNQDVINAVEQDYRLPPPMDCPTALHQLM
HEK11 CKVSDFGLSRVIEDD.PEAVYT.TTGGKIPVRWTAPEAIQYRKFTSASDVWSYGIVMWEVMSYGERPYWDMSNQDVIKAIEEGYRLPAPMDCPAGLHQLM
          *                                   ∞

CONS  ldCWqk.RnrRPkF.qivniLdklirnpnSLktia.assr.s.pLld.sgpd.ttfrtvgeWLeaikmgryke.Ftaagyts..avaqmtaeDl.riGvt
EPH   KNCWAYDRARRPHFQKLQAHLEQLLANPHSLRTIANFDPRVTLRLPSLSGSDGIPYRTVSEWLESIRMKRYILHFHSAGLDTMECVLELTAEDLTQMGIT
ECK   MQCWQQERARRPKFADIVSILDKLIRAPDSLKTLADFDPRVSIRLPSTSGSEGVPFRTVSEWLESIKMQQYTEHFMAAGYTAIEKVVQMTNDDIKRIGVR
HEK4  LDCWQKDRNNRPKFEQIVSILDKLIRNPGSLKIITSAAARPSNLLLDQSNVDISTFRTTGDWLNGVRTAHCKEIFTGVEYSSCDTIAKISTDDMKKVGVT
HEK5  LDCWQKDRNHRPKFGQIVNTLDKMIRNPNSLKAMAPLSSGINLPLLDRTIPDYTSFNTVDEWLEAIKMGQYKESFANAGFTSFDVVSQMMMEDILRVGVT
HEK7  LDCWQKERNSRPKFDEIVNMLDKLIRNPSSLKTLVNASCRVSNLLAEHSPLGSGAYRSVGEWLEAIKMGRYTEIFMENGYSSMDAVAQVTLEDLRRLGVT
HEK8  LDCWQKERSDRPKFGQIVNMLDKLIRNPNSLKRTGTESSRPNTALLDPSSPEFSAVVSVGDWLQAIKMDRYKDNFTAAGYTTLEAVVHVNQEDLARIGIT
HEK2  LDCWVRDRNLRPKFSQIVNTLDKLIRNAASLKVIASAQSGMSQPLLDRTVPDYTTFTTVGDWLDAIKMGRYKESFVSAGFASFDLVAQMTAEDLLRIGVT
HEK11 LDCWQKERAERPKFEQIVGILDKMIRNPNSLKTPLGTCSRPISPLLDQNTPDFTTFCSVGEWLQAIKMERYKDNFTAAGYNSLESVARMTIEDVMSLGIT
```

FIG. 5F

```
CONS   lvghQkkIlsSiq.mr.Qmnqgh.p.v.V
EPH    LPGHQKRILCSIQGFKD
ECK    LPGHQKRIAYSLLGLKDQVNTVGIPI
HEK4   VVGPQKKIISSIKALETQSKNGPVPV
HEK5   LAGHQKKILNSIQVMRAQMNQIQSVEV
HEK7   LVGHQKKIMNSLQEMKVQLVNGMVPL
HEK8   AITHQNKILSSVQAMRTQMQQMHGRMVPV
HEK2   LAGHQKKILSSIQDMRLQMNQTLPVQV
HEK11  LVGHQKKIMSSIQTMRAQMLHLHGTGIQV
```

FIG. 6

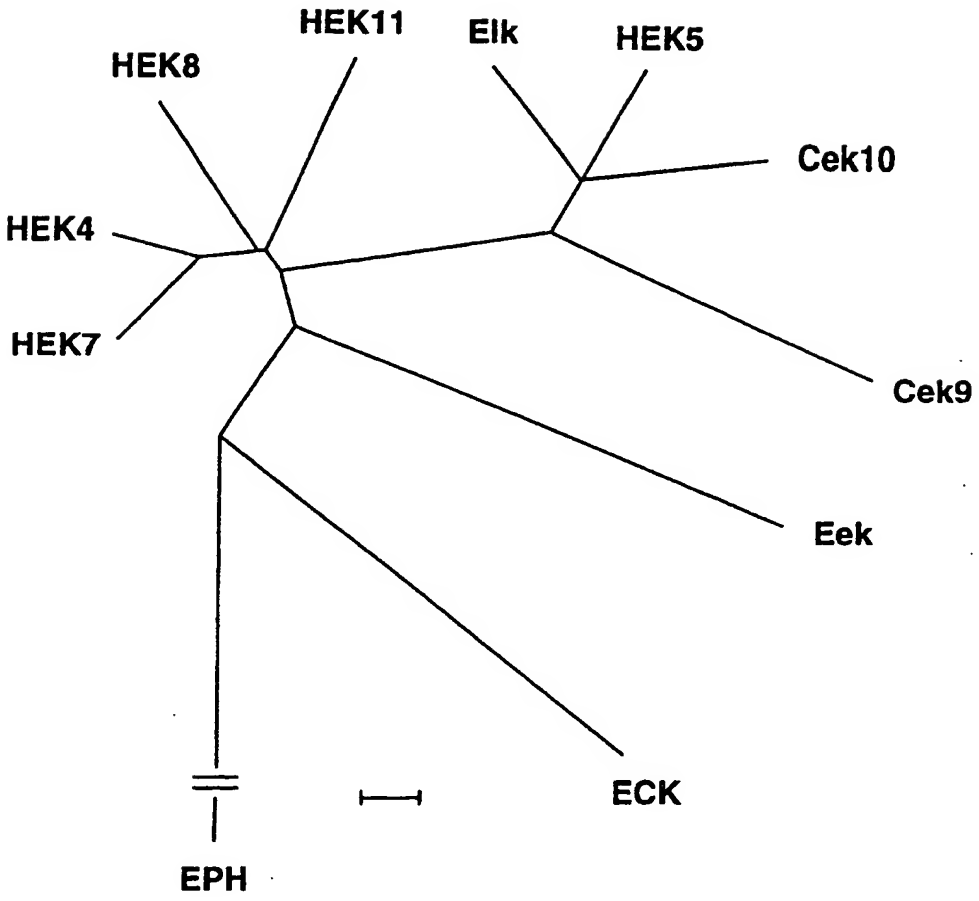


FIG. 7A

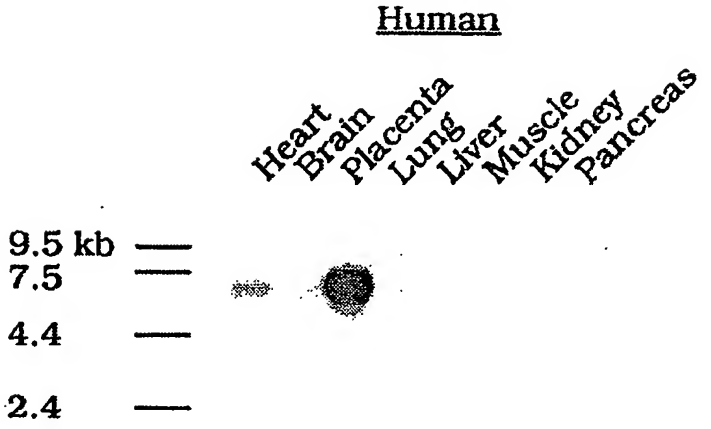

Human
Heart
Brain
Placenta
Lung
Liver
Muscle
Kidney
Pancreas
9.5 kb
7.5
4.4
2.4

FIG. 7B

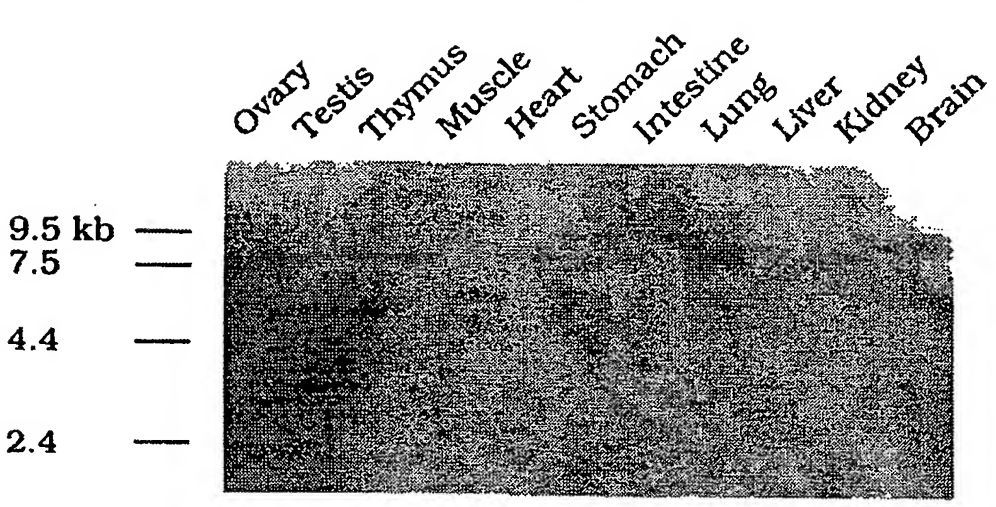

Rat
Ovary
Testis
Thymus
Muscle
Heart
Stomach
Intestine
Lung
Liver
Kidney
Brain
9.5 kb
7.5
4.4
2.4

FIG. 8A

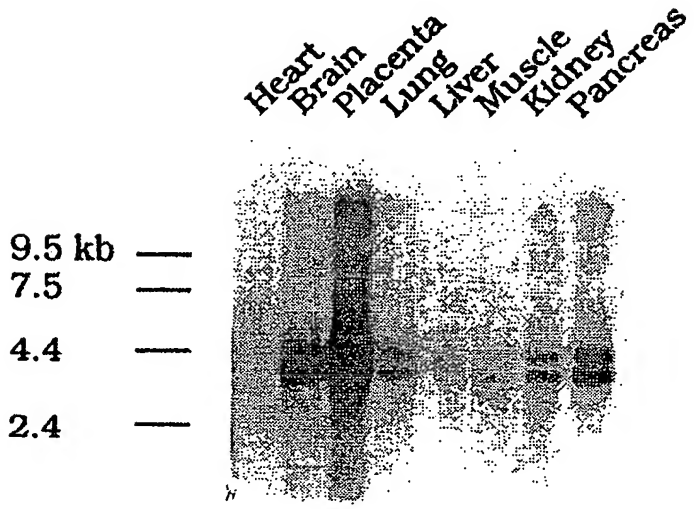

Human
Heart
Brain
Placenta
Lung
Liver
Muscle
Kidney
Pancreas
9.5 kb
7.5
4.4
2.4

FIG. 8B

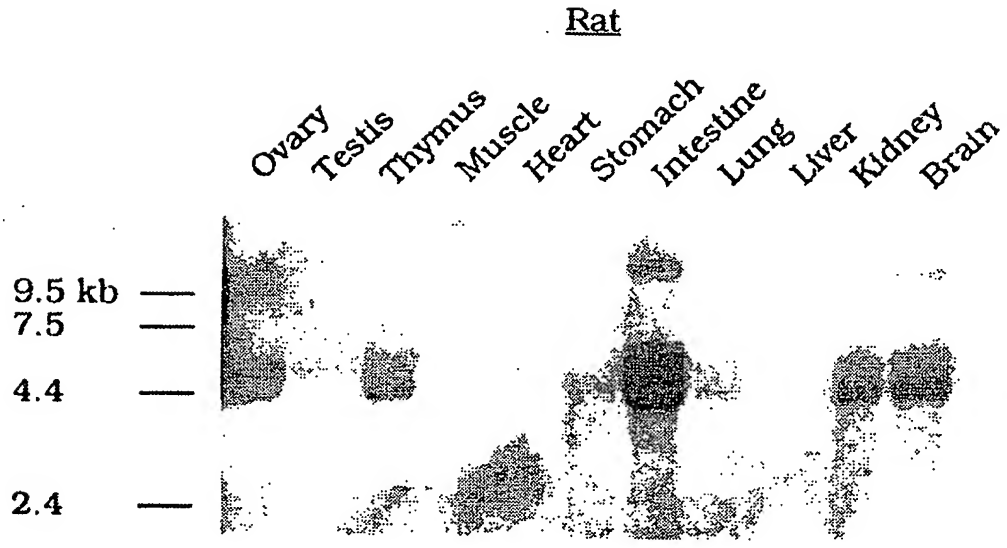

Rat
Ovary
Testis
Thymus
Muscle
Heart
Stomach
Intestine
Lung
Liver
Kidney
Brain
9.5 kb
7.5
4.4
2.4

FIG. 9A

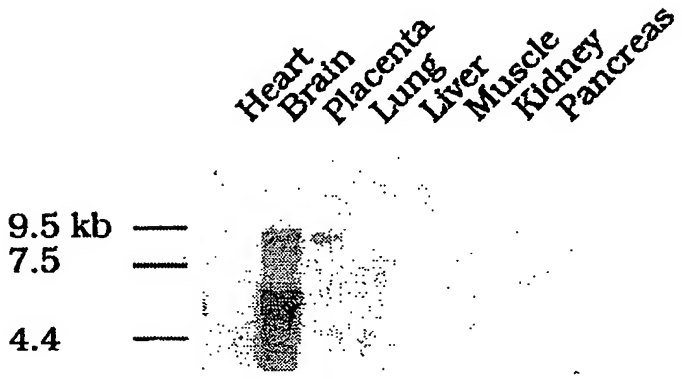

Human
Heart
Brain
Placenta
Lung
Liver
Muscle
Kidney
Pancreas
9.5 kb
7.5
4.4

FIG. 9B

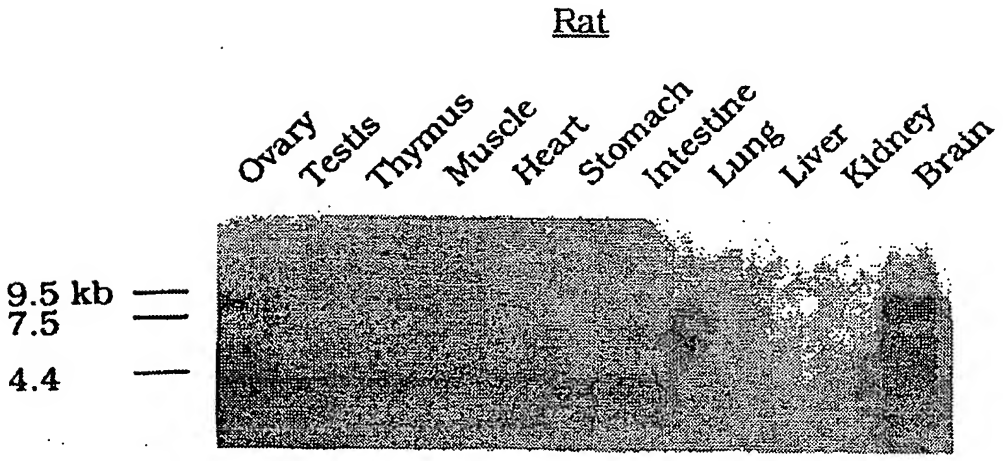

Rat
Ovary
Testis
Thymus
Muscle
Heart
Stomach
Intestine
Lung
Liver
Kidney
Brain
9.5 kb
7.5
4.4

FIG. 10A

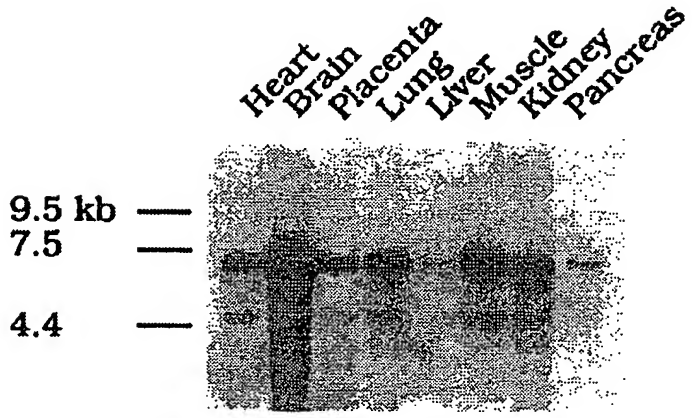


FIG. 10B

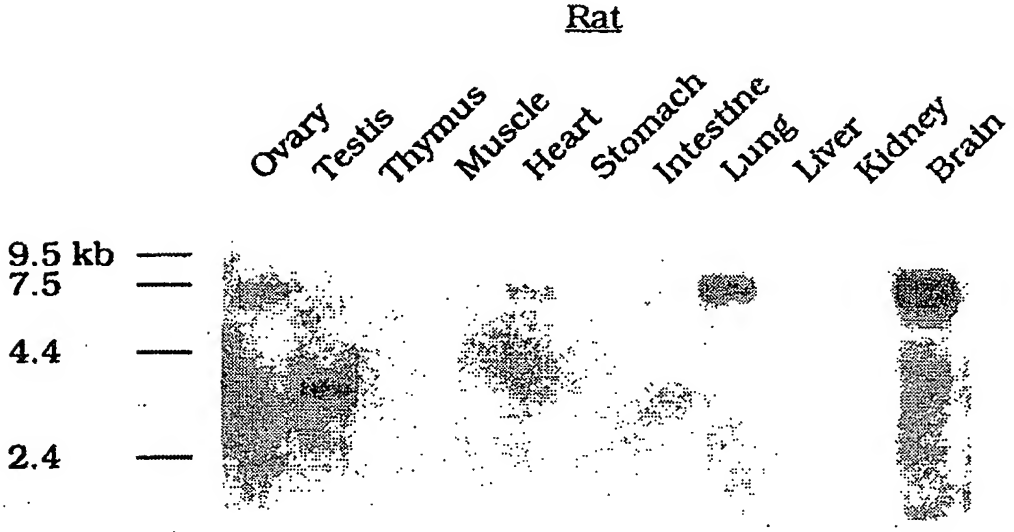


FIG. 11A

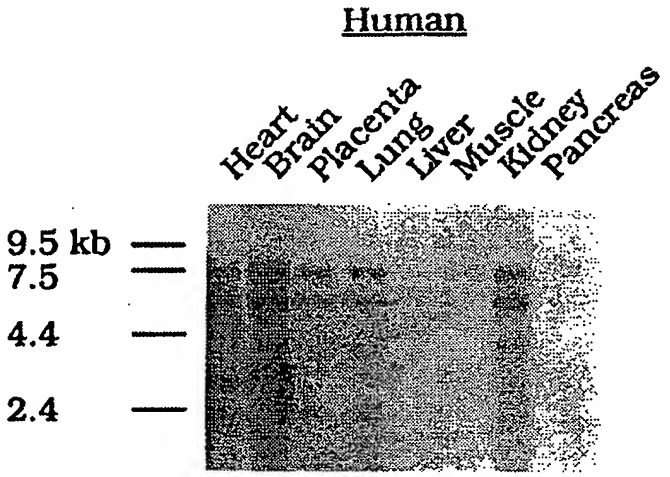
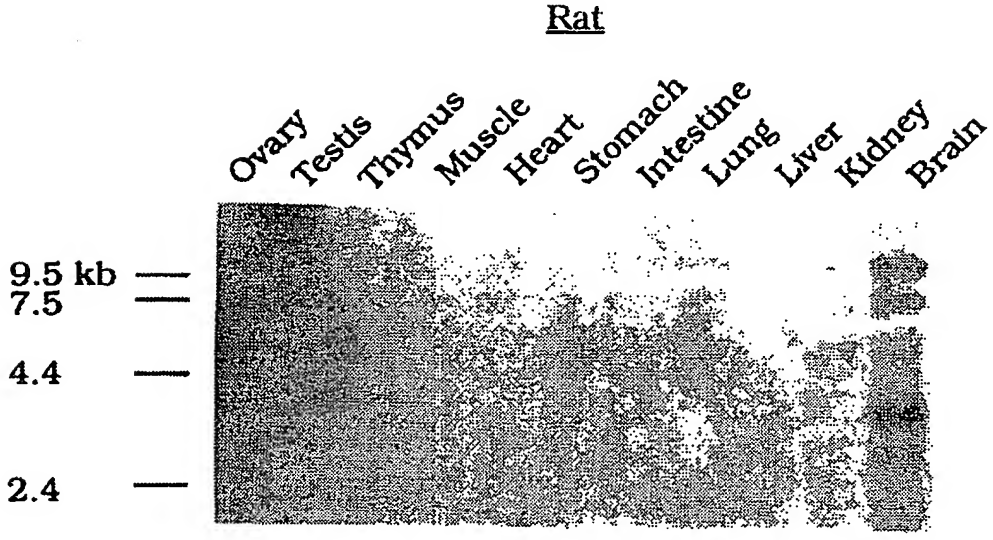


FIG. 11B



INTERNATIONAL SEARCH REPORT

[redacted] ial Application No
[redacted]/US 95/04681

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/71 C07K16/28 A61K38/17 A61K39/395
C12N15/62 G01N33/566

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO-A-93 00425 (INST MEDICAL W & E HALL) 7 January 1993 see the whole document ---	1-8,10, 15-18, 20,23, 25-32,34
X	DE-A-42 33 782 (CHEMOTHERAPEUTISCHES FORSCHUNG) 14 April 1994 see the whole document ---	1-9, 15-19, 23, 25-32,34
X	CA-A-2 083 521 (MOUNT SINAI HOSPITAL CORP) 1 October 1993 see the whole document ---	1-7,13, 15-18, 23-32,34
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 September 1995	15. 09. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Nauche, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ONCOGENE, vol. 7, no. 12, December 1992 pages 2499-2506, HEBENSTREIT-GILARDI, P. ET AL.; 'An Eph-related receptor tyrosine kinase gene segmentally expressed in the developing mouse hindbrain.' see the whole document	1-8,11, 15-18, 21,23, 25-27,34
X	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 194, 1993 ORLANDO, FL US, pages 698-705, IWASE T., TANAKA M., SUZUKI M., NAITO Y., SUGIMURA H.; 'Identification of protein-tyrosine kinase genes preferentially expressed in embryo stomach and gastric cancer' see the whole document	1-9, 15-19, 23, 25-27, 32,34
X	CELL REGULATION, vol. 2, July 1991 pages 523-534, PASQUALE, E.B.; 'Identification of chicken embryo kinase 5, a developmentally regulated receptor-type tyrosine kinase of the Eph family' see the whole document	1-9, 15-19, 23, 25-29, 32,34
X	ONCOGENE, vol. 8, 1993 pages 1807-1813, SAJJADI F.G., PASQUALE E.B.; 'Five novel avian Eph-related tyrosine kinases are differentially expressed' see the whole document	1-11, 15-21, 23, 25-27, 32,34
X	BRITISH JOURNAL OF CANCER, vol. 69, no. 3, March 1994 pages 417-421, TUZI NL;GULLICK WJ; 'eph, the largest known family of putative growth factor receptors.' see the whole document	1-11, 13-21, 23-27, 32,34
X	ONCOGENE, vol. 8, no. 12, December 1993 pages 3277-3288, MAISONPIERRE PC;BARREZUETA NX;YANCOPOULOS GD; 'Ehk-1 and Ehk-2: two novel members of the Eph receptor-like tyrosine kinase family with distinctive structures and and neuronal expression.' cited in the application see the whole document	1-8,10, 15-18, 20,23, 25-27, 32,34

-/--

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ONCOGENE, vol. 6, no. 6, 1991 pages 1057-1061, CHAN, J.; WATT, V.M.; 'eek and erk, new members of the eph subclass of receptor protein-tyrosine kinases' cited in the application see the whole document ---	1-9, 15-18, 23, 25-27, 32,34
X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 89, no. 5, 1 March 1992 WASHINGTON US, pages 1611-1615, WICKS IP;WILKINSON D;SALVARIS E;BOYD AW; 'Molecular cloning of HEK, the gene encoding a receptor tyrosine kinase expressed by human lymphoid tumor cell lines.' cited in the application see the whole document ---	1-8,12, 15-18, 22-27, 32,34
P,X	ONCOGENE, vol. 10, no. 5, 2 March 1995 pages 897-905, FOX GM;HOLST PL;CHUTE HT;LINDBERG RA;JANSSEN AM;BASU R;WELCHER AA; 'cDNA cloning and tissue distribution of five human eph-like receptor protein-tyrosine kinases' see the whole document -----	1-34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 95/04681

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 32
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 32 is directed to a method of treatment of the human/animal body (Rule 39.1(iv)) PCT), the search has been carried out and based on the alleged effects of the compound/ composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9300425	07-01-93	AU-B- 655299	15-12-94
		EP-A- 0590030	06-04-94
		JP-T- 6508747	06-10-94
DE-A-4233782	14-04-94	NONE	
CA-A-2083521		NONE	